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## METABOLIC STUDIES IN PERNICIOUS ANEMIA \*

R B GIBSON, PH D AND C P HOWARD, M D

IOWA CITY

It should require considerable courage to add to the voluminous literature on the pathogenesis and chemistry of the so-called idiopathic pernicious anemia of Addison and Biermer. Our excuse is a threefold one —first, to investigate with the aid of modern microchemical methods the metabolism of the blood lipoids as of probable diagnostic if not of etiological significance, second, to determine the nitrogen metabolism both in regard to its diagnostic as well as its prognostic value, and, third, to test the efficiency of Whipple's high iron diet when given to patients suffering from idiopathic anemia.

We have had the opportunity to study eleven cases of pernicious anemia, several of which have been available for considerable periods of time or during subsequent admissions. As controls, and in order to obtain comparative data on the anemias, four additional cases have been employed, a case of aplastic anemia with von Recklinghausen's disease, a pregnancy anemia, a hemolytic icterus case, and a splenic anemia.

### 1 GENERAL PROCEDURE

Each patient, after the usual clinical and laboratory investigation had established definitely the diagnosis, was transferred from the general medical ward to the special metabolic unit. There were available a special dietitian and two graduate nurses experienced in metabolic work. In this way a reasonable assurance can be given that the food intake and urine and fecal collections were carefully controlled.

Two diets have been employed in all except our earliest metabolic runs. These included fruits, green vegetables, lima beans, sweet potatoes, egg yolk and liver (daily), the constituents being selected to provide a ration rich in iron, and relatively low in fat. Diet 1 contained 10.64 gm nitrogen and 45.6 mg iron (by Wolter's modification of Neumann's method<sup>1</sup>) and yielded about 1900 calories. Diet 2 contained 12.04 gm nitrogen, 26.9 mg iron, and was equivalent to about

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\* From the Medical Clinic and the Research Laboratory of the Medical Clinic of the University Hospital, the State University of Iowa.

1 Wolter, O. Ueber das Harn Eisen I. Die Bestimmung des Eisens im Harn, *Biochem Ztschr* **24** 108-124, 1910.

1,500 calories This diet was planned for patients who could not consume completely the previous diet, or it was used increased by half at other times Correction was made for extraneous iron in charcoal given to differentiate stools and in a yeast vitamin preparation used Food not consumed was analyzed, and allowance made accordingly While the iron values we have obtained for these diets are higher than the calculated values from the commonly available food tables, our figures were checked on diets prepared at different times and by several analysts, iron determinations on the urine and stools were made by the same method An adequate vitamin supply and sufficient cholesterol, which is easily absorbed (Knudsen<sup>2</sup>) are provided in such a ration, cholesterol may have especial significance because of the low blood content of this substance in pernicious anemia along with its known antihemolytic action The diets, in a way, are in accord with Thompson's recommendations<sup>3</sup> with a consideration of the work of Whipple and his associates on blood regeneration

Blood samples for the study of the blood and plasma lipins were taken at the beginning and conclusion of the metabolic periods, and at such other times as the blood counts or the clinical course of the cases made further observations of interest

Further details as to procedure will be given in the appropriate sections of this paper

## 2 PLASMA AND BLOOD LIPINS WITH ESPECIAL REFERENCE TO IODIN ABSORPTION VALUES IN PERNICIOUS ANEMIA

The investigations of Schaumann,<sup>4</sup> Tallquist<sup>5</sup> and Faust<sup>6</sup> on the lipid hemolytic substances of *Bothriocephalus latus* have had a profound influence on our views as to the origin of pernicious anemia These investigators apparently proved conclusively that the active hemolytic substance is oleic acid (present in the worm as the cholesterol ester which made up 10 per cent of the solids of the proglottides of

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2 Knudson, A Relationship Between Cholesterol and Cholesterol Esters in the Blood During Their Absorption, J Biol Chem **45** 255-262, 1921

3 Carter, H S, Howe, P E, and Mason, H H Diet in Blood Diseases, Nutrition and Clinical Dietetics, Philadelphia, Lea & Febiger, Ed 2, 1921, p 536

4 Schauman, O, and Tallquist, T W Ueber die blutkoerperchenaufloesenden Eigenschaften des breiten Bandwurms, Deutsch med Wchnschr **24** 312-313, 1898

5 Tallquist, T W Zur Pathogenese der perniziösen Anaemie mit bes Beruecksichtigung der Bothriocephalusanaemie, Ztschr f klin Med **61** 427-532, 1907

6 Faust, E S, and Tallquist, T W Ueber die Ursachen der Bothriocephalusanaemie, Arch f exper Path u Pharmacol **57** 367-385, 1907

Faust, E S Ueber chronische Oelsaurevergiftung, Arch f exper Path u Pharmacol Suppl Vol 1908, pp 171-175

the parasites) The "lipoid substance" was strongly hemolytic in vitro When injected into dogs and rabbits, it gave rather disappointing results, producing only a mild and transitory anemia of the secondary type, in fact, the anemia was so slight as to be attributable by impartial critics of the protocols to inanition and anorexia following the administration of any toxic substance Further, it was discovered by Schmincke and Flury <sup>7</sup> that the dog's red cells acquired an immunity in vitro as well as in vivo to the hemolytic action of oleic acid It is true that two years later Adler <sup>8</sup> reported the production in rabbits of blood crises resembling those of pernicious anemia by feeding nontoxic amounts of olive oil and cottonseed oil, both of which are, needless to say, rich in unsaturated fatty acids A careful study of Adler's protocols, however, leaves one as nonenthusiastic, if not as entirely unconvinced, as did those of Faust and Tallquist Joannovics and Pick <sup>9</sup> also attempted to explain hemolytic anemia by oleate hemolysis They showed that as the result of subacute toluyldiamin poisoning in the dog, the ether soluble hemolytic substance (chiefly oleic acid) is increased in the liver to at least forty or fifty times the normal They also found <sup>10</sup> in acute yellow atrophy and in phosphorus poisoning in man and animals that hemolysins of great activity could be obtained from the liver and that fatty acids could be found in large quantities in the blood They explained the hemolytic effects of liver extracts in these conditions as due to the unsaturated fatty acid content

Beumer and Burger,<sup>11</sup> from their studies of the blood in pernicious anemia, chlorosis, leukemia and icterus, considered that the quantitative relations of the lipoids in the serum and corpuscles were of significance They do not consider it definitely proven that the gastro-intestinal mucosa contains lipoids capable of producing anemia

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7 Schmincke, A, und Flury, F Ueber das Verhalten der Erythrocyten bei chronischen Oelsauerevergiftung, Arch f exper Path u Pharmakol **64** 126-140, 1911

8 Adler, H J The Experimental Production of Pernicious Anemia in Rabbits, J M Research **23** 199-226, 1913

9 Joannovics, G, and Pick, E P Beitrag zur Kenntniss der Toluyldiaminvergiftung, Ztschr f exper Path. u Therap **7** 185-214, 1909

10 Joannovics, G, and Pick, E P Ueber haemolytischwirkende freie Fettsauren in den Leber bei akuten gelber Atrophie und Phosphorvergiftung, Berl klin Wchnschr **47** 928-930, 1910

11 Buerger, M, and Beumer, H Zur Lipoidschemie des Blutes I Ueber die Verteilung von Cholesterin, Cholesterinestern und Lecithin in Serum, Berl klin Wchnschr **50** 112-114, 1913

Beumer, H, and Buerger, M II Ueber die Zusammensetzung der Stromata menschlichen Erythrocyten mit besonderer Beruecksichtigung der Lipoide, Arch f exper Path u Pharmak **71** 311-328, 1913

Beumer, H, and Buerger, M Beitrage zur Chemie des Blutes in Krankheiten mit besonderer Beruecksichtigung der Lipoide III Mitteilung, Ztschr f exper Path u Therap **13** 343-361, 1913



McPhedran<sup>12</sup> has demonstrated in a very convincing manner that the idea that toxic hemolysis in disease, in poisoning by phosphorus or toluylendiamin results from the liberation of specially hemolytic fatty acids from the fatty complexes of disintegrating cells is not well supported by evidence, none of the fatty acids, still less any of the fatty complexes from which these acids can be obtained in any of the organs examined, either in this work or in the work of others that has preceded it show on analysis any evidence for the existence of fatty acids more toxic than the common oleic acid which is constantly being set free by hydrolysis from common fat in health

More recently Seyderhelm<sup>13</sup> has shown that it is not the lipid fraction of the *gastrophilus* larvae (present in the stomach of the horse) nor of the *bothriocephalus proglottis* that is hemolytic in the body of the host, the alcoholic precipitate, however, is strongly hemolytic to the red cells of rabbits when introduced parenterally, though inactive *in vitro*. The composition of this blood poison is not given by Seyderhelm, but he has named it according to its origin "oestrin" and "bothriocephalin"

Finally, Beumer<sup>14</sup> has again tested out the hemolytic action of oleic acid by feeding young dogs (3 weeks old) in the belief that they might be more susceptible. As a matter of fact, the two dogs so tested revealed no anemia

However, before the necessary time had elapsed to permit of the repetition and control of Faust and Tallquist's experiments, attempts were repeatedly made to assign the phenomena of idiopathic anemia to the presence of a powerful hemolysin circulating in the body presumably of a nonsaturated fatty acid nature. Consequently, the attention of the clinical investigators was directed to the study of the lipoids of the blood. Eppinger<sup>15</sup> in collaboration with King<sup>16</sup> and Medak<sup>17</sup> reported an increase in the total blood fats above the normal, while the free cholesterol was decreased to varying degrees. "The striking finding however, was the very high value for the iodine numbers. It is significant that the blood with the highest iodine number showed the lowest value in free cholesterol" (King). While the findings of Eppinger, King, and Medak as regards the low cholesterol figures have been sub-

12 McPhedran, W. F. On the Hemolytic Properties of Fatty Acids and Their Relation to the Causation of Toxic Hemolysis and Pernicious Anemia, *J. Exper. Med.* **18** 527-542, 1913

13 Seyderhelm, R. Zur Pathogenese der pernicioesen Anaemia, *Deutsch. Arch. f. klin. Med.* **126** 95-147, 1918

14 Beumer, H. Zur pathogenetischen Bedeutung der Oelsaure bei Anaemien, *Biochem. Ztschr.* **95** 239-248, 1919

15 Eppinger, H. Zur Pathologie der Milzfunktion (I Mitteilung), *Berl. klin. Wchnschr.* **50** 1509-1512, 1572-1576, 1913

16 King, J. H. Studies in the Pathology of the Spleen, *Arch. Int. Med.* **14** 145-167 (Aug.) 1914

17 Medak, E. Beitrag zur Chemie des Blutes bei anaemischen Krankheitbildern, *Bioch. Ztschr.* **59** 419-428, 1914

stantiated by Feigl<sup>18</sup> and by Rosenthal and Holzer<sup>19</sup> in Germany, and by Csonka,<sup>20</sup> Bloor and MacPherson,<sup>21</sup> Denis<sup>22</sup> and Kipp<sup>23</sup> in America, their conclusions have not escaped the criticism of Feigl and of Rosenthal and Holzer as one might expect from McPhedran's observations previously quoted. The main cause for criticism is the high iodine number for the blood fat found by Eppinger et al. However, if one takes into account the definite statement that the iodine values are multiplied by ten with the probable purpose to establish a pro mille basis, then figures are not actually high as compared with those of other observers. Yet one must admit that Eppinger et al. considered them abnormally high and stated that their results "suggested that hemolysis was due to the unsaturated fatty acids." At the beginning of our work, we felt in accord with Bloor and MacPherson who wrote that "While the results offer no certain evidence that abnormalities in the blood lipoids are responsible for anemia, the low values of the cholesterol, which is an antihemolytic substance, and the high fat fraction, which may indicate the presence of abnormal amounts of hemolytic lipoids in the blood, are possible causative factors, of which further investigation is desirable."

We have made iodine absorption, fatty acid and cholesterol determinations on the whole blood and plasma in our series of cases. For the iodine values, one of us (Gibson) has adapted the Hanus method for micro-analysis, using the filtrates from the Bloor blood fat extraction after the fat and cholesterol (Autenrieth and Funk) have been determined. We have thus been able to obtain figures for the nonsaturated fatty acid groups at more frequent intervals than if we had to employ large quantities of blood for the usual determination of the iodine number.

Three cubic centimeters of whole blood or plasma are extracted with alcohol-ether mixture and the filtrates made up to 100 c.c. as in Bloor's method.<sup>21</sup> Duplicate extractions are made. Ten cubic centimeters from each extraction are used for nephelometric determination of the blood fat, and 10 c.c. more for the cholesterol. The 80 c.c. remaining are evaporated in a glass dish on the steam bath, and removed just as dryness is reached. The residues are washed three times with 10 c.c. of chloroform, each time pouring through small filters into 100 c.c.

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18 Feigl, J. Ueber das Vorkommen und die Verteilung von Fetten und Lipoiden in menschlichen Blute bei toxaemischen (haematinaemischen) Krankheit Zuständen, *Bioch. Ztschr.* **93** 257-288, 1919.

19 Rosenthal, F., und Holzer, P. Beitrage zur Chemie des Blutes bei anaemischen Krankheitszuständen, *Biochem. Ztschr.* **108** 220-234, 1920.

20 Csonka, F. A. A Critique of Certain Data on the Content of Cholesterol and Fatty Substances in the Blood, etc., *J. Biol. Chem.* **24** 431-438, 1916.

21 Bloor, W. R., and MacPherson, D. J. The Blood Lipoids in Anemia, *J. Biol. Chem.* **31** 79-95, 1917.

22 Denis, W. Cholesterol in Human Blood Under Pathologic Conditions, *J. Biol. Chem.* **29** 93-110, 1917.

23 Kipp, H. A. The Effect of Whole Blood Transfusion on the Cholesterol Content of Human Serum in Pernicious Anemia, *J. Biol. Chem.* **43** 413-420, 1920.

**Ehrlenmeyer flasks** The flasks are then placed on the steam bath and evaporated just to dryness, so that when removed from the bath enough chloroform condenses within the flask to take up the fat residues. One c c of chloroform is added to each flask and to three control flasks, 2 c c exactly of Hanus' iodine solution is introduced into each one of the series, the contents thoroughly mixed by rotating, corked and placed in a dark locker for one hour. Fortieth normal sodium thiosulphate solution is used for the titration after adding 0.5 c c of 15 per cent potassium iodide solution and 10 c c of water, with starch paste employed as an indicator toward the end of the titration in the usual way. The titration difference  $\times 0.305$  divided by the grams of fat in the alcohol-ether extract used equals the iodine number. The iodine absorbed per 100 c c of blood may be taken as an indication of the non-saturated fatty acid groups present.

We did not find, as did King and also Bloor, abnormally high blood fats in our pernicious anemia cases (Table 1). In fact, very low blood and plasma fat contents accompanied the severe anemic condition in Cases 1, 4, 10 and 11, and these were increased with improvement in the blood picture. Very small fat figures have been found in pernicious anemia (two cases studied) by Denis<sup>24</sup> also. The low blood fats seem to be associated with higher iodine numbers in the pernicious anemia cases, though the amounts of the unsaturated fatty acid groups as evidenced by the total iodine absorbed were small. Case 7, with a red blood cell count of less than one million and a hemoglobin of 25 per cent, had a normal fat, iodine number of 64, and the iodine absorbed was 0.43 gm per 100 c c of blood, very similar figures obtain for Case 6 with an anemia of mild degree only. The highest concentration of non-saturated fatty acid groups (0.86 gm) appears in the aplastic anemia case (Case 12) in the analysis of the whole blood sample for March 7.

Blood and plasma cholesterol figures were low in the pernicious anemia cases with pronounced anemia, and tended to increase to normal as the blood regenerated. High cholesterol figures were found for Case 6, a patient with marked cord changes, but with a mild degree of anemia only. Three out of the four pathologic control cases (Cases 12, 13 and 14) showed a normal or high cholesterol, it is of particular interest that the fourth control (Case 15), a case of splenic anemia, had low plasma and blood cholesterol figures.

We consider that our results are in accord with Feigl's as well as Rosenthal and Holzner's observations.

While our results indicate that an increase in the unsaturated fatty acids in the blood cannot be a factor for hemolysis in pernicious anemia, the problem has been attacked in a different way. Recently Ashby<sup>25</sup>

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24 Denis, W. The Influence of Splenectomy on Metabolism in Anemia, *Arch Int Med* **20** 79-92 (July) 1917.

25 Ashby, W. Study of Transfused Blood, *J Exper Med* **34** 127-146, 147-166, 1921.

TABLE 1—*Fat, Cholesterol and Iodine Absorption Vaults for Whole Blood and Plasma*

Case	Date	R B C	Hbg	R B C Pl	Plasma				Blood			
					Chol	Fat	I <sub>2</sub> , No	I <sub>2</sub> , %	Chol	Fat	I <sub>2</sub> , No	I <sub>2</sub> , %
1 McG Pernicious anemia	2/24/20	1,910	40						0 10	0 34	72	0 37
	3/19/20	2,000	50						0 58	87	0 50	
	10/12/20	930	25					0 07	0 53	41	0 22	
	10/16/20	660	18					0 08	0 35	53	0 19	
	12/10/20	2 900	70		0 17	0 68	59	0 40				
2 M'd Pernicious anemia	4/19/20	1,970	65						0 15	0 50	73	0 36
3 Mn Pernicious anemia	4/10/20	2,400	70						0 18	0 51	88	0 45
4 Mat Pernicious anemia	12/ 9/20	1,290	30	9 91	0 11	0 25			0 15	0 29	95	0 27
	12/22/20	1,980	40	21 79	0 15	0 63	53	0 33		0 45	60	0 27
	1/ 8/21	1,790	47	30 70	0 17	0 55	60	0 33		0 49	73	0 35
	1/24/21	2,640	78	33 67	0 21	0 50	51	0 26				
	2/ 1/21	3,170	65						0 26	0 58	56	0 32
	3/ 7/21	3,120	80	30 70	0 19	0 50	88	0 44	0 22	0 60	73	0 44
5 Baugh Pernicious anemia	1/18/21	3,080	74	30 70	0 19	0 67	30	0 20				
	2/ 7/21	2,910	70		0 16	0 50	56	0 28	0 18	0 60	65	0 39
6 Blbg Pernicious anemia, splenectomy	1/25/21	4 030	85	40 60	0 27	0 70	40	0 28				
	2/ 1/21	4,520	92						0 28	0 67	66	0 44
	3/ 7/21	4,290	100	46 54	0 25	0 81	65	0 53	0 29	0 70	68	0 47
	5/10/21	4,800	100	45 55	0 29	0 65	80	0 52	0 32	0 65	94	0 54
	8/16/21	5,280	95		0 31	0 68	74	0 50	0 27	0 70	88	0 62
7 W Pernicious anemia	3/22/21	990	25	11 89	0 14	0 53	75	0 41	0 16	0 67	64	0 43
8 Dug Pernicious anemia	10/22/21	2,620	54	32 68	0 21	0 67	95	0 65	0 18	0 60	107	0 64
	10/30/21	3 260	68		0 16	0 67	81	0 54	0 19	0 63	80	0 50
	11/ 7/21	3 180	70	38 62	0 16	0 67	71	0 48	0 19	0 58	86	0 50
	11/29/21	4 050	80	42 58	0 21	0 89	71	0 41	0 25	0 60	87	0 52
9 Mill Pernicious anemia	11/ 7/21	2,180	50	26 64	0 21	0 64	82	0 49	0 20	0 46	109	0 50
	11/15/21	2,210	50		0 19	0 52	86	0 40	0 20	0 46	85	0 44
	11/22/21	2,790	65	39 61	0 16	0 51	70	0 41	0 23	0 65	81	0 46
	11/29/21	2,820	65		0 16	0 57	89	0 51	0 17	0 62	82	0 51
10 Sch Pernicious anemia	12/ 5/21	925	23	17 83	0 09	0 35	101	0 36	0 14	0 47	77	0 36
	12/12/21	1,410	35	25 75	0 11	0 37	85	0 32	0 17	0 34	101	0 35
	12/19/21	2,620	56	26 74	0 20	0 55	78	0 43	0 17	0 54	77	0 42
11 Han Pernicious anemia, syphilis	3/30/22	1,110	26	13 87	0 002	0 35	65	0 23	0 16	0 38	63	0 24
	4/ 3/22	1,020	30	18 82	0 14	0 39	99	0 40	0 18	0 63	65	0 44
	4/ 7/22	2,200	44	21 79	0 16	0 41	89	0 30	0 15	0 35	108	0 38
12 Boy Aplastic anemia	12/22/20	3,600	45		0 30	0 50	60	0 33		0 62	63	0 41
	2/ 7/21	3,590	40		0 20	0 62	47	0 29	0 21	0 77	54	0 42
	3/ 7/21	4,320	65	33 67	0 33	0 72	76	0 54	0 44	0 90	93	0 86
13 Cook Pregnancy, anemia	3/ 1/21	1,690	40	16 84	0 21	0 57	80	0 47	0 27	0 58	82	0 48
	3/ 9/21	1,320	45	19 81	0 19	0 39	94	0 36	0 22	0 44	84	0 37
	3/18/21	2,550	43	21 79	0 20	0 52	70	0 36	0 24	0 58	71	0 43
14 Hel Hemolytic icterus, splenectomy	2/17/21	4,444	92	48 52	0 29	0 64	83	0 53	0 38	0 65	90	0 59
15 Plom Splenic anemia	12/ 5/21	2,600	40	20 80	0 09	0 44	70	0 40	0 15	0 54	73	0 40
	12/10/21		32	18 82	0 09	0 31	92	0 29	0 10	0 34	84	0 29
	12/17/21	1,480	30									

studied the length of life of transfused corpuscles in pernicious anemia and concluded that there was no hemolytic toxin producing the anemia in this disease. Wearn, Warren and Ames<sup>26</sup> have confirmed Ashby's experimental observations, though conservatively questioning her conclusion. They have found also in a single observation that red blood corpuscles from a patient with pernicious anemia when transfused into another patient with pernicious anemia behaved as did the corpuscles from normal donors.

### 3 NITROGEN AND IRON BALANCES AND THE NITROGEN PARTITION

Metabolic studies on pernicious anemia were first directed to the nitrogen balance. Neither von Noorden<sup>27</sup> nor Halpern<sup>28</sup> was able to show that protein catabolism was increased characteristically in this condition, while Rosenquist<sup>29</sup> found periods in which increased nitrogen excretion and retention alternated. According to Mohr,<sup>30</sup> a nitrogen retention may obtain in some cases even on a low protein intake, and in others a loss of nitrogen may be observed when a high protein diet is given, the nitrogen exchange is not dependent on the diminution of the hemoglobin. The difficulty in obtaining nitrogen balances is evident in the later contributions on the anemias with or without splenic disease (Umber,<sup>31</sup> Minot,<sup>32</sup> McKelvey and Rosenbloom,<sup>33</sup> Goldschmidt and Pearce,<sup>34</sup> Goldschmidt, Pepper and Pearce,<sup>35</sup> Pepper and Austin<sup>36</sup>)

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26 Wearn, J. T., Warren, S., and Ames, O. The Length of Life of Transfused Erythrocytes in Patients with Primary and Secondary Anemia, *Arch Int Med* **29** 527-538 (May) 1922

27 Cited by Strauss, H. Der Einfluss der Blutkrankheiten auf die Eiweisszersetzung der Purinkörper und Salzstoffwechsel, v. Noordens Handb. d. Path. u. Stoffwechsels. Berlin, A. Hirschwald, **1** 891-895, 1906

28 Halpern, M. Zur Frage der Stickstoffvertheilung im Harn in pathologischen Zuständen, *Ztschr. f. klin. Med.* **50** 355-376, 1903

29 Rosenquist, E. Ueber den Eiweissstoffwechsel bei der pernicioesen Anaemie, *Ztschr. f. klin. Med.* **49** 193-320, 1903

30 Mohr, L. Gesamtstoffwechsel bei Anaemien, Kachexien, u. s. w. Handb. d. Biochem. d. Menschen u. d. Thiere. Jena, G. Fischer, **4** 381-392, 1910

31 Umber, F. Zur Pathogenese der Bantischen Krankheit mit besonderer Berücksichtigung des Stoffumsatzes, u. s. w., *Ztschr. f. klin. Med.* **55** 289-314, 1904

32 Minot, G. R. Nitrogen Metabolism Before and After Splenectomy, etc., *Bull. Johns Hopkins Hosp.* **26** 338-342, 1914

33 McKelvey, J. P., and Rosenbloom, J. Metabolism Study of a Case of Hemolytic Jaundice, etc., *Arch Int Med* **15** 227-238 (Feb.) 1915

34 Goldschmidt, S., and Pearce, R. M. Studies of Metabolism in the Dog Before and After Removal of the Spleen, *J. Exper. Med.* **22** 319-331, 1915

35 Goldschmidt, S., Pepper, O. H. P., and Pearce, R. M. Metabolism Studies Before and After Splenectomy in Congenital Hemolytic Icterus, *Arch Int Med* **16** 437-455 (Sept.) 1915

36 Pepper, O. H. P., and Austin, J. H. Metabolism Studies Before and After Splenectomy in a Case of Pernicious Anemia, *Arch Int Med* **18** 131-135 (July) 1916

though slight nitrogen retention may occur. Positive nitrogen balances are indicated in Denis' <sup>24</sup> series of anemia cases, both before and after splenectomy, the diet was high caloric but low in protein. Mosenthal <sup>27</sup> readily obtained a favorable nitrogen balance with improvement in the blood picture for three cases of pernicious anemia and one case of secondary anemia when given high protein and energy diets.

Von Noorden found a lower percentage of the total nitrogen excretion as urea nitrogen for some cases, though he cites higher figures from earlier workers. Minot's case before transfusion and splenectomy had a very low urea nitrogen elimination—on one day only 34.5 per cent of a total nitrogen of 14.6 gm. Figures cited by von Noorden from the older literature for the ammonia nitrogen excretion are normal or relatively low, ammonia nitrogen averaged 0.42 gm per day in Minot's case and still less in Denis' cases. Uric acid elimination is variable, Rosenquist reporting minimal and maximal purin nitrogen (endogenous) of from 0.173 to 0.409 gm. In the later literature, Pepper and Austin and also Denis give uric acid figures for pernicious anemia, the daily excretion may be rather high, but not abnormally so. Kahn and Barsky <sup>38</sup> consider the nitrogen fractions of the urine normal, except for an increased elimination of oxyproteic acid nitrogen, conjugated sulphates and neutral sulphur were increased.

As the result of splenectomy preceded by a transfusion, the slightly negative nitrogen balance in Minot's case was changed over to a slight retention, the urea nitrogen was increased from an average of 54.3 per cent to 79.6 per cent of the total nitrogen, but there was no change in the ammonia nitrogen excretion. Pepper and Austin obtained a more favorable nitrogen balance and a drop in the uric acid excretion as the result of transfusion and splenectomy, the daily iron elimination in the stool fell from 17 to 10 mg. The effects of splenectomy were not constant in Denis' observations, nor were the sulphur partition figures significant.

Gettler and Lindeman <sup>39</sup> found in thirty-two cases of pernicious anemia blood and nonprotein nitrogen, urea nitrogen, and creatinin values higher than normal, uric acid figures were quite high, and the amino-acid nitrogen was increased also. The blood sugar, too, was abnormally high.

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<sup>37</sup> Mosenthal, H. O. The Effect of Forced Feeding on the Nitrogen Equilibrium and Blood in Pernicious Anemia, *Bull. Johns Hopkins Hosp.* **29** 129-134, 1918.

<sup>38</sup> Kahn, M., and Barsky, J. Studies of the Chemistry of Pernicious Anemia, *Arch. Int. Med.* **23** 334-345 (March) 1919.

<sup>39</sup> Gettler, A. O., and Lindeman, E. Blood Chemistry of Pernicious Anemia, *Arch. Int. Med.* **26** 453-458 (Oct.) 1920.

Peters and Rubnitz<sup>40</sup> determined the total nitrogens of the whole blood and of the blood plasma of four cases of pernicious anemia, the determination of course includes the protein nitrogen. Inasmuch as the corpuscles are richer in total nitrogen content than the plasma, the total nitrogen of which remains within normal limits or tends to increase, they establish a "nitrogen index" or ratio of the whole blood nitrogen to the plasma nitrogen, this is diminished in proportion to the degree of anemia and may therefore be used as an indication of the state and progress of the anemic condition.

Our own work has been directed chiefly to the study of the nitrogen and iron balances when the "pernicious anemia diet" was given, figures on the nitrogen partition were also obtained. These data are summarized in Table 2. Figures are averages of four or five day periods. No medication was employed while the patients were in the metabolism unit, and the diet was given two or three days or longer previous to actually starting the balance runs. The commonly used analytical procedures were followed for the determinations of the nitrogen partition. Because of the undigested food residues frequently appearing in the pernicious anemia stools and due to the characteristically deficient gastric secretion, it was necessary to use the dried and thoroughly ground feces for analysis.

The total nitrogen elimination is not excessive. On a very moderate protein intake of from 61 to 75.5 gm. and with a relatively low calorie value, Cases 2, 3, 4 (Period 1), 6 (Period 2, after splenectomy), 7, 8 (Period 2) and 9 have given positive nitrogen balances. Cases 10 and 11, on a higher protein intake, have eliminated a greater amount of nitrogen, as might be expected, but have shown a favorable balance. Slight or moderate nitrogen losses obtained for Cases 1, 4 (Periods 2 and 3), 6 (Period 1) and 8 (Period 2), while a considerable nitrogen excretion and loss occurred for Case 5. Of the controls, Case 14 (hemolytic icterus) showed consistently a negative nitrogen balance, though the nitrogen excretion was markedly diminished in the post-splenectomy Period 3, the diets for Periods 1 and 3 were probably too low in calories, the patient being a large man and active at these times.

In the case of the iron balances, it might be expected that the results would be influenced by the deposition in or discharge of stored iron from the tissues. However, the iron balances quite consistently follow the gain, the stationary state or the fall in blood cell counts and hemoglobin percentages. Thus favorable iron balances were observed for Cases 1 (Period 2), 2, 4, 5, 6 (increased after splen-

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40 Peters, A. W., and Rubnitz, A. S. Observations on the Chemical Pathology of the Blood in Pernicious Anemia, *Arch. Int. Med.* **26**: 561-569 (Oct.) 1920.

TABLE 2—Nitrogen and Iron Balances and Nitrogen Partition

Case	Period	Total N, Gm	Urea N		Ammonia N		Uric Acid N		Creatinin N		Balances		Food						
			Gm	%	Gm	%	Gm	%	Gm	%	N, Gm	Fe, Mg	Prot., Gm	Fat, Gm	Obhy, Gm	Total, Cal	Fe, Mg		
1 McG	1 2/17-21/20	8.75					0.350	4.36	0.326	3.74	0.022	0.26	-0.21	-6.3	61	34	284	1,684	27.7
	2 3/4-8/20	8.80					0.393	4.46	0.292	3.34	0.049	0.54	-0.59	+4.3*	61	34	284	1,684	27.7
	3 10/13-15/20	12.16	7.90	65.0	0.482	3.97	0.307	2.53	0.468	3.85	0.189	1.55			†				
2 M'd	1 4/16-19/20	10.57	7.54	71.3	0.620	5.87	0.289	2.73	0.427	4.13	0.000	0.00	+0.47	+10.7*	74	64	276	1,977	42.4
	2 5/11-14/20	9.80	7.99	81.5	0.701	7.15	0.244	2.49	0.411	4.20	0.000	0.00	+1.59	+21.3	75	50	324	2,052	35.2
	3 4/7-10/20	8.09	6.62	81.7	0.530	6.55	0.283	3.50	0.338	4.18	0.000	0.00	+1.57	+0.1	62	45	231	1,570	24.0
4 Mat	1 12/19-22/20	9.38	6.64	70.8	0.388	4.13	0.596	6.35	0.402	4.28	0.000	0.00	+0.06	+22.6	67.5	39.6	305	1,896	45.6
	2 2/7-12/21	9.75	7.45	76.6	0.427	4.38	0.228	2.34	0.376	3.86	0.050	0.51	-1.13	+1.5	67.5	39.6	305	1,896	45.6
	3 4/9-14/21	9.50	6.97	71.5	0.332	3.49	0.233	2.45	0.396	4.17	0.021	0.22	-1.45	+10.5	67.5	39.6	305	1,896	45.6
5 Baugh	1 1/19-24/21	12.49	8.52	68.3	0.528	4.23	0.374	3.00	0.503	4.03	0.037	0.45	-3.47	+7.7	67.5	39.6	305	1,896	45.6
	1 1/25-29/21	8.78	6.21	70.7	0.532	6.06	0.229	2.61	0.574	6.54	0.054	0.61	-0.81	+2.3	67.5	39.6	305	1,896	45.6
	2 5/12-17/21†	6.45	3.85	61.1	0.270	4.19	0.148	2.30	0.585	9.00	0.000	0.00	+2.24	+12.4	67.5	39.6	305	1,896	45.6
7 W	1 5/3-8/21	5.44	2.81	51.7	0.353	6.49	0.265	4.86	0.120	2.21	0.043	0.79	+3.37	+23.3	67.5	39.6	305	1,896	45.6
	1 10/26-29/21	8.34	7.00	83.90	0.586	7.04	0.211	2.60	0.269	3.23	0.000	0.00	+0.15	-32.9	67.5	39.6	305	1,896	45.6
	2 11/2-6/21	8.85	6.51	73.62	0.687	7.77	0.181	2.04	0.271	3.07	0.000	0.00	-0.21	-8.5	68	68.6	305	2,167	49.7
9 Mill	1 11/9-11/21	7.05	5.64	80.60	0.670	11.97	0.154	2.24	0.170	3.04	0.000	0.00	+0.36	+16.2	67.6	39.6	304	1,896	45.6
	2 11/15-19/21	9.78					0.185		0.185				+0.47	+1.1	75.4	35	205.7	1,521	35.8
	3 11/23-27/21	9.98					0.178		0.178						75.1	70	205.7	1,816	35.8
10 Sch	1 12/7-12/21	7.17	5.03	70.18	0.366	5.10	0.275	3.83	0.289	4.03	0.000	0.00			75.4	70	205.7	1,846	35.8
	2 12/17-20/21	9.04	6.95	76.86	0.479	5.31	0.228	2.53	0.233	2.58	0.000	0.00			75.4	70	205.7	1,846	35.8
	3 12/21-24/21	9.25	7.28	78.81	0.525	5.68	0.231	2.50	0.239	2.58	0.000	0.00	+2.30	+0.7	113	53	307	2,157	50.0
	4 1/12-16/22	13.71					0.228		0.228				+1.28	-5.3	113	88	307	2,172	46.0
	5 1/16-19/22	14.60					0.276		0.276										
11 Han	1 3/31-4/3/22	14.21					0.340		0.366		0.027		+2.10	+13.4	113	53	307	2,157	43.7
	2 4/4-7/22	14.38	11.98	83.31	0.479	3.33	0.390	2.71	0.375	2.61	0.000	0.00	+2.13	+16.6	113	88	307	2,172	42.3
12 Boy	1 12/19-22/20	6.81	4.37	63.7	0.637	9.35	0.373	5.47	0.314	4.61	0.022	0.32	+1.79	+21.8	67.5	39.6	305	1,896	45.6
	1 3/2-5/21	6.96	4.84	69.5	0.360	5.17	0.333	4.78	0.324	4.63	0.068	0.98	-0.45	+1.6	67.5	39.6	305	1,896	45.6
	2 3/9-14/21	9.29	6.93	74.6	0.245	2.64	0.390	4.20	0.350	3.88	0.091	0.87	+1.51	+3.8	67.5	39.6	305	1,896	45.6
14 Hel	1 2/3-7/20	14.14	10.99	77.7	0.699	4.94	0.194	1.37	0.677	4.79	0.000	0.00	-1.06	+13.7	79	111	208	2,152	29.7
	2 3/1-5/20†	15.18					0.317	2.09	0.543	3.57	0.000	0.00	-2.81	+5.2	79	111	208	2,152	29.7
	3 2/17-20/21	11.47	8.28	72.2	0.516	4.50	0.212	1.85	0.585	5.10	0.038	0.33	-1.67	+25.0	67.5	39.6	305	1,896	45.6
15 Plom	1 11/30-12/4/21	8.83	7.65	86.6	1.012	11.35	0.212	2.40	0.394	4.46	0.000	0.00	+0.55	-1.7	67.5	39.6	305	1,896	45.6
	2 12/8-13/21#	8.52					0.250		0.405						67.5	39.6	305	1,896	45.6

\* Iron balances in these starred figures are from food and stool determinations, the urines were not done or were lost in these cases It is probable the urines did not contain over a milligram or two per diem  
† Very little eaten ‡ A little refused § Splenectomy ¶ After gout attack



ectomy), 7, 9 and 11, with coincident betterment of the blood picture. Approximate iron equilibrium was found for Case 3 and for case 10 when little change in the blood findings obtained. Case 8 exceptionally presented a considerable loss of iron during the first period and a much less figure for the second period, an increase in the blood count with little change in the hemoglobin percentage was recorded at this time. The nonpernicious anemia cases all showed favorable iron balances except the splenic anemia case, for which a slight iron loss of 17 mg per day was noted. That positive iron balances may accompany a daily loss of nitrogen to the body is shown in the data for Cases 1 (Period 2), 4 (Periods 2 and 3), 5 and 6 (Period 1), and for the nonpernicious Cases 13 (Period 1) and 14.

In four of our studied cases of pernicious anemia (Cases 8, 9, 10 and 11) we have tried the effect of the addition of a moderate amount of fat to the diet. In view of a possible marked stimulation of hemolysis—though not indicated by our blood studies—we have employed butter as the source of the fat since this has a moderate iodine absorption value only. The less favorable figures obtained for Cases 9 and 10 suggest that further investigation of fat ingestion in pernicious anemia should be carried out.

As regards the nitrogen partition, the pernicious anemia cases tend to show low urea nitrogen figures. Moderate or low ammonia nitrogen figures may be found—Cases 1, 4, 5, 6 after splenectomy, 7, 10 and 11. Rather high uric acid nitrogen figures obtain, even when the patients were on a nonpurin diet (Cases 1, 2 and 3), exceptions are Case 6 after splenectomy, Case 8 (Period 2), and Case 9. Of the other anemias, the aplastic Case 12 presented a nitrogen partition similar to that of pernicious anemia, except for the ammonia figures, while the pregnancy anemia Case 13 is quite suggestive of the pernicious anemia findings. The hemolytic icterus Case 14 gave a low urea nitrogen percentage of the total nitrogen, but the other constituents are normal for Period 1, an ultimate effect of splenectomy is not reflected in the nitrogen partition figures for Period 3. The splenic anemia Case 15 picture was characterized by a high ammonia excretion only, following an attack of gout, the uric acid elimination was somewhat increased.

Our findings may be summarized briefly for this section. Favorable nitrogen, and especially iron, balances have been established in pernicious anemia and in some other types of clinical anemias (excepting iron in our case of splenic anemia) when given diets rich in food iron and with comparatively low calorie and protein values. Slightly negative nitrogen balances and coincident iron retention may obtain. Low urea nitrogen excretion and low or moderate ammonia nitrogens along

with rather high uric acid nitrogen figures are characteristic but not constant findings, these results are in general accord with most of the figures available in the literature

#### 4 IMMEDIATE EFFECTS OF BLOOD TRANSFUSION ON METABOLISM

Cases 1 and 2 were transfused with from 450 to 500 c c of blood (citratd) of the same grouping while under observation in the metabolism unit. The immediate effect of the transfusion was a pronounced stimulation of the nitrogen catabolism. The increased excretion of the total, urea, uric acid and creatinin nitrogens continued over the succeeding two days. The figures are given in Table 3.

TABLE 3—*Effects of Transfusion of Blood of Similar Grouping*

Case	Period	Total N, Gm	Urea N, Gm	Am monia N, Gm	Uric Acid N, Gm	Creat- inin N, Gm	Crea- tin N, Gm	Food			
								Pro tein, Gm	Fat, Gm	Chy- ly, Gm	Total, Cal
1 McG (1)	2/22/20	8.06			0.389	0.279	0.007	62	32	285	1,679
	2/23/20	8.86			0.391	0.274	0.045	63	35	253	1,575
	2/24/20*	9.52			0.383	0.353	0.050	52	23	245	1,401
	2/25/20	10.92			0.459	0.334	0.058	63	35	307	1,792
	2/26/20	12.42			0.370	0.305	0.102	62	36	302	1,781
	2/27/20	10.08			0.408	0.285	0.022	62	39	281	1,524
2 Md	4/24-27/20	8.27	6.50	0.440	0.276	0.437	0.000	64	44	294	1,877
	4/28/20*	5.25	3.61	0.284	0.185	0.434	0.000	†			
	4/29/20	13.72	10.12	0.435	0.324	0.570	0.000	39	40	161	1,160
	4/30/20	13.89	11.53	0.435	0.404	0.471	0.000	64	51	234	1,650

\* Transfused

† Breakfast only

#### 5 FAT UTILIZATION AND STOOL FATS IN ANEMIA CASES

We present some data on the food and stools fat, including the iodine absorption numbers, and the utilization of the ingested fat in this series of cases. The results are given in Table 4.

Sherman<sup>41</sup> gives the average normal fat utilization or "coefficient of digestibility" as 95 per cent. Of course, this factor varies with the amount of fat in the diet, since diets free from fat yield stools which contain appreciable amounts of ether soluble substances. In view of this fact, a utilization of fat of from 72 to 89 per cent by our pernicious anemia cases is very satisfactory.

There is no definable relation between the character or degree of the anemia and the partition or the iodine values of the stool fats. Though considerable variation was found, the iodine numbers were all comparatively low. While it is probable that the iodine values of the stool fats have been lessened because of the dessication of the stools for the nitrogen and iron determinations, the food fats were subjected to

41 Sherman, H. C. Comparative Digestibility of Fats, Foods Products, New York, McMillan & Co, 1917, p. 393.

the same procedure, again, iodine numbers obtained on the lipin extracts of a fresh stool (Case 1, Period 3) were quite similar to the other values obtained. Our data afford no evidence of the intestinal formation of fatty acids of high iodine values in pernicious anemia.

## DISCUSSION

Dietetic deficiency in the sense of avitaminosis has not been considered an etiologic factor in pernicious anemia, though Fayrer<sup>42</sup> (in 1888) suggested that pernicious anemia in Europe resembled beriberi.

TABLE 4—*Fat Utilization and Stool Fats in Anemia Cases*  
(The fat analyses are in percentages of the dried feces)

Case	Period	1 Total Fat	2 Neu- tral Fat	3 Free Acids	4 Soap Acids	5 Total Acids	Per Cent Split	Per Cent Util- ized	Iodine Nos for		
									1	2+3	Food Fat
1 McG	1	19.71	4.37	6.77	8.57	15.34	77.8	70.3	17.2	30.4	64.5
	2	21.05	5.09	7.06	8.90	15.96	71.1	73.2	18.6	32.3	64.5
	3	22.14*	7.57	4.61	9.88	14.57	65.8			30.6	
2 M'd	1	33.69	13.47	12.00	8.22	20.22	60.0	72.3	13.82	18.3	63.9
	2	31.54	10.28	14.13	7.13	21.26	67.4	78.2	18.1	26.0	69.9
4 Mat	1	26.62	15.97	5.08	5.57	10.65	40.0	80.0	4.0	5.1	60.9
	2	24.86	15.05	6.43	3.38	9.81	39.5	73.0		24.4	60.9
5 Bgh	1	21.04	10.33	3.95	6.79	10.74	50.9	79.2		33.6	60.9
8 Dug	1	21.4	13.5	4.0	3.9	7.9	36.9	82.8			
	2†	23.9	14.8	5.7	3.4	9.1	38.0	88.7			
9 Mill	1	29.1	14.3	12.3	2.5	14.8	50.7	84.4			
	2†	32.2	16.9	12.1	3.2	15.3	47.2	83.4			
10 Sch	4	22.6	7.2	8.4	7.0	15.4	68.1	83.5			
	5†	28.0	11.0	12.0	5.8	17.8	63.5	88.5			
12 Boy	1	17.78	13.06	3.00	1.72	4.72	26.5	76.9	30.67	33.9	60.9
13 Cook	1	14.90	6.80	4.65	3.44	8.09	54.3	88.3		40.4	60.9
	2	16.92	10.92	3.10	2.90	6.00	35.5	87.8		40.6	60.9
14 Hel	3	17.63	14.21	2.03	1.37	3.40	19.4	89.0		35.9	60.9
15 Plom	1	24.3	13.0	5.9	6.4	12.2	50.3	77.4			

\* Fat extractions made on the fresh stool.

† The fat ingestion was doubled in these periods over the preceding periods.

in the Orient. According to Castellani and Chalmers,<sup>43</sup> beriberi shows a certain degree of anemia, with leukopenia and a diminished number of polymorphonuclear leukocytes. Again, secondary anemia may occur in infantile scurvy (Hess<sup>44</sup>), in pellagra (Hillman<sup>45</sup>), as the result of

42 Fayrer, J. Beriberi, Quain's Dictionary Medicine, London, 1888, p 104.

43 Castellani, A., and Chalmers, A. J. Beri-beri and Epidemic Dropsy, Manual of Tropical Medicine. New York, Wm Wood & Co., Ed 3, 1919, pp 1686-1687.

44 Hess, A. F. Infantile Scurvy the Blood Vessels and the Diet, Am J Dis Child 8 385-405, 1914.

45 Hillman, O. S. Some Hematologic Findings in Pellagra, Am J M Sc 145 507-513, 1913.

continued reduced diets (Benedict <sup>46</sup>), and in rice fed rabbits (Downs and Eddy <sup>47</sup>) As yet we have little information as to whether or not vitamins play any part in hematogenesis Vitamin deficiency may well be a predisposing factor for the acute exacerbation and may delay the onset and progress of the remissions in pernicious anemia

For the limited number of cases reported here in which we have given adequate and iron rich diets, we have found little difficulty in establishing favorable iron balances along with clinical improvement and lessened recourse to transfusion Our results would tend to confirm those of Whipple and his associates,<sup>48</sup> who found that in experimental hemorrhagic anemia in dogs, blood regeneration is hastened on a diet containing meat, liver, or other iron rich foods However, Musser <sup>49</sup> has found that his dogs rendered anemic by repeated small bleedings were not so amenable to a high iron diet, he frankly admits that the factor of damaged blood formation in the clinical anemias of man was not of course present in either Whipple's or his own dogs We realize that caution must be exercised in concluding from our few cases that an iron rich diet hastens blood regeneration in pernicious anemia where spontaneous remissions may occur And while we may suggest that every effort should be made to have the patients consume such a diet in the hospital and that they should receive instructions as to diet when discharged, we still feel justified in continuing the administration of iron in the form of Bland's pills and arsenic as Fowler's solution

#### SUMMARY

Eleven cases of pernicious anemia, and for comparative data, one case each of an aplastic anemia, pregnancy anemia, hemolytic icterus and splenic anemia, have been studied

Low whole blood and plasma fats were found in the severe pernicious anemia cases and tended to increase with improvement in the blood picture for the individual cases The low blood fats seem to be associated with higher iodin numbers (by a micro-adaptation of the Hanus method) though the amounts of the unsaturated fatty acid groups as evidenced by the total iodin absorbed are not excessive An increased

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46 Benedict, F G, et al Human Vitality and Efficiency Under Prolonged Restricted Diet, Washington, Carnegie Inst, 1919, Pub No 280

47 Downs, A W, and Eddy, N B Secretin V Its Effects in Anemia, Am J Physiol 58 296-300, 1921

48 Whipple, G H, Robscheit, F S, and Hooper, C W Blood Regeneration Following Simple Anemia IV Influence of Meat, Liver and Various Extractives Alone or Combined with Standard Diets, Am J Physiol 53. 236-262, 1920

49 Musser, J H, Jr. The Influence of Inorganic Iron on the Regeneration of Blood After Hemorrhagic Anemia, Arch Int Med 28 638-648 (Nov) 1921

unsaturated fatty acid content, therefore, should not be a factor for hemolysis in pernicious anemia

That blood and plasma cholesterol figures are low in pernicious anemia cases and increase as the blood is regenerated is confirmed. Low figures were found also for one splenic anemia case.

More favorable nitrogen and especially iron balances may be readily established in pernicious anemia and some other anemias (excepting iron in our case of splenic anemia) when diets rich in food iron (Whipple) and comparatively low in calorie and protein values are given. Negative nitrogen balances and coincident iron retention may obtain.

Characteristic but not constant alterations in the nitrogen partition in pernicious anemia are low urea and moderate ammonia nitrogens, and high uric acid figures. The immediate effects of blood transfusions on the daily nitrogen partition (two cases) are an increase in the total, urea, uric acid, and creatinine nitrogen elimination, persisting over at least two days.

A fat utilization of from 72 to 89 per cent in our pernicious anemia cases is quite satisfactory when the low fat of the diet is considered. Our data furnish no evidence of the intestinal formation of fatty acids or of high iodine absorption values.

In view of our experience, the use of iron-rich and vitamin adequate diets in the anemias is urged, but we do not feel that established therapeutic measures to promote hematogenesis should be neglected.

# BLOOD PRESSURES IN FIFTEEN THOUSAND UNIVERSITY FRESHMEN \*

WALTER C ALVAREZ, M D

Assisted by

ROSALIND WULZEN AND LUCILLE J MAHONEY

SAN FRANCISCO

About two years ago one of us (WCA) published a number of observations based on a statistical study of nearly 9,000 blood pressure records made on the incoming freshmen at the Students' Infirmary of the University of California<sup>1</sup>. That analysis led to a number of conclusions which were so surprising and so contrary to all previous teachings that the need was felt for further study with a larger series of data. In the first place, it was found that hypertension is not a disease of old age alone, it is found commonly among young people, healthy enough to go to college. Furthermore, the pressure does not increase with age as we have always thought. The average actually drops from the age of 17 to 21 in the men, and from 17 to 25 in women. After that, it stays about the same among the men until after 50, among the women it rises quite rapidly after 25, and very rapidly after 40. The result is that although the young women's pressures average 10 mm or more below the young men's, after 45, so far as our data go, the women actually average higher than the men. It is interesting also to note the marked difference between the amount of hypertension among the girls and boys. It appears earlier in the boys and is often quite high. Thus, one 18 year old boy was found with a pressure exceeding 215 mm.

It was hard to believe at first that there could be so much hypertension among presumably healthy young men, but a comparison of our data with some data obtained by Barach and Marks, Lee, some of the insurance examiners, and some of the army physicians showed that very similar observations had been made elsewhere<sup>1</sup>.

A careful statistical analysis of the figures showed that those for the women were probably quite accurate and trustworthy, their distribution curves were fairly smooth, and the yearly averages for the 1919 freshmen were almost identical with those for the 1918 freshmen<sup>2</sup>.

The figures for the men were not so satisfactory, partly because the examiners showed a strong tendency to read to the nearest multiple

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\* From the George Williams Hooper Foundation for Medical Research, University of California Medical School and the University Infirmary

1 Alvarez Arch Int Med 26 381 (Sept) 1920

2 A few of the data classed under the heading 1918 were secured in 1916 and 1917

TABLE 1—Blood Pressure Observations on Men Students

Pressure	Ages												Total	Per- cent- age	Per- cent ages Smoothed	Pressure
	16	17	18	19	20	21	22	23	24	25 to 26	27 to 30	31 to 35	36 to 40			
85-89													5	0.08	0.15	85-89
90-94		1	3	3	4		1	2	3	1	3	2	18	0.30	0.36	90-94
95-99	1	2	2	3	8		10	5	5	2	5	1	38	0.61	0.82	95-99
100-104	1	3	14	17	20	15	6	6	5	5	8	3	89	1.48	1.44	100-104
105-109	1	11	16	16	20	15	6	6	5	5	8	3	122	2.03	3.65	105-109
110-114	6	40	79	87	41	52	36	26	18	29	17	12	447	7.45	7.15	110-114
115-119	9	49	116	105	78	59	47	37	26	36	36	18	622	10.37	12.50	115-119
120-124	21	97	249	204	143	136	89	64	47	59	49	23	1,196	19.96	12.31	120-124
125-129	9	57	124	125	69	66	49	49	20	36	26	14	650	10.85	14.60	125-129
130-134	17	103	232	190	166	106	65	57	45	60	34	28	1,104	18.41	13.60	130-134
135-139	9	57	100	84	49	43	33	22	20	19	12	10	464	7.74	7.91	135-139
140-144	11	54	122	115	83	59	42	34	22	23	21	11	605	10.08	8.85	140-144
145-149	3	27	44	30	26	12	12	4	7	8	7	3	179	9.23	4.81	145-149
150-154	3	15	57	44	23	22	17	11	9	8	4	2	218	3.63	3.24	150-154
155-159	3	8	20	11	12	11	7	2	4	1	1	2	77	1.23	2.02	155-159
160-164		7	22	9	9	7	6	8	5	8	6	1	93	1.55	1.35	160-164
165-169		3	4	3	3	8	1	2	4	2	1	1	29	0.48	0.74	165-169
170-174		4	5	3	3	5	1	3	5	2	1	2	23	0.38	0.43	170-174
175-179		1	1	1	1	1	1	3		3			10	0.16	0.23	175-179
180-184		1	1	1	1	1	1						7	0.11	0.11	180-184
185-189		1	1	1	1	1							2	0.02	0.01	185-189
190-194													1	0.01	0.01	190-194
195-199																195-199
200-204																200-204
205-209																205-209
210-214																210-214
215-219																215-219
Total	94	541	1,216	1,066	742	623	422	335	231	299	232	130	6,000		0.01	
Mean	129.3	130.1	130.0	128.2	129.5	127.6	128.3	129.1	129.0	128.3	127.0	127.0	128.9			
Standard deviation	12.5	13.2	13.1	13.0	13.6	13.8	12.8	13.9	12.6	14.1	14.0	13.2	13.5			
Standard deviation of the mean	1.29	0.57	0.38	0.40	0.50	0.55	0.62	0.76	0.83	0.81	0.92	1.07	1.28			
Probable error of the mean	0.87	0.38	0.25	0.27	0.33	0.37	0.42	0.51	0.56	0.54	0.62	0.72	1.54			
Median	128.5	129.0	129.0	127.4	129.0	125.6	126.3	126.8	128.0	126.2	124.0	126.5	127.6			
Mode (calculated)	129.9	126.8	127.0	125.8	128.0	121.6	122.3	122.9	126.0	122.0	118.0	125.5	121.0			
Coefficient of variation	9.7	10.1	10.3	10.1	10.5	10.8	10.0	10.7	10.6	11.0	11.0	9.6	10.6			
Measure of skewness	0.19	0.25	0.22	0.18	0.11	0.43	0.47	0.50	0.24	0.45	0.64	0.13	0.31			
Percentage over 130 mm	49	52	50	46	50	43	43	43	48	43	38	44	47			
Percentage over 140 mm	21	22	23	20	22	19	20	20	20	17	18	14	20			

TABLE 2—Blood Pressure Observations on Women Students

Pressure	Ages												Total	Per- cent- age	Per- cent- age Smoothed	Pressure
	16	17	18	19	20	21	22	23	24	25 to 26	27 to 30	31 to 35	36 to 40			
80-84	1		2	5	2	1	1	2	1	2	1	8	6	0.06	0.06	80-84
85-89		7	4	15	7	2	4	5	2	2	2	8	20	0.22	0.28	85-89
90-94	1	30	20	31	18	3	17	11	9	10	14	30	67	0.75	1.03	90-94
95-99	6		40	40	72	19	48	40	20	45	51	45	221	2.47	3.50	95-99
100-104	12	72	158	117	83	53	73	43	29	37	69	84	743	8.24	11.74	100-104
105-109	22	92	166	145	187	167	88	70	84	88	109	84	870	9.75	12.99	105-109
110-114	29	186	431	318	187	167	68	63	57	74	79	57	1,872	20.98	42.47	110-114
115-119	25	154	285	221	162	106	68	63	44	70	98	28	1,379	15.45	57.92	115-119
120-124	41	210	379	319	175	141	79	78	44	88	109	84	1,758	17.21	77.62	120-124
125-129	18	109	206	152	84	59	41	40	20	25	51	25	655	10.80	87.19	125-129
130-134	17	88	151	97	58	49	35	13	25	28	44	36	242	7.35	94.54	130-134
135-139	10	25	64	42	24	15	12	8	4	8	8	14	159	2.72	97.26	135-139
140-144	3	21	36	23	16	6	7	9	2	5	4	15	36	1.79	99.05	140-144
145-149		5	9	7	4	4	1	1	1	1	2	2	12	0.40	99.45	145-149
150-154		2	4	5	3	3	1	3	1	2	2	2	30	0.33	99.78	150-154
155-159		2	2	1	1	4	1	1	1	1	1	1	12	0.13	99.91	155-159
160-164		1	1	1	1	1	1	1	1	1	1	1	3	0.03	99.94	160-164
165-169													2	0.02	99.96	165-169
170-174													1	0.01	99.97	170-174
175-179													1	0.01	99.98	175-179
180-184			1										1	0.01	99.99	180-184
185-189			1										1	0.01	100.00	185-189
Total	185	1,004	1,661	1,498	895	701	447	387	299	397	536	399	8,934			
Mean	118.0	118.1	117.7	117.3	117.2	116.7	116.3	116.4	116.1	116.1	116.6	118.2	117.3			
Standard deviation	10.9	10.7	11.0	10.4	10.3	10.1	10.7	11.1	9.8	10.5	11.0	10.9	10.8			
Standard deviation of the mean	0.80	0.84	0.25	0.27	0.34	0.38	0.50	0.57	0.57	0.53	0.48	0.55	0.11			
Probable error of the mean	0.50	0.23	0.17	0.18	0.23	0.25	0.33	0.38	0.38	0.35	0.32	0.37	0.08			
Median	118.0	117.7	116.8	116.7	116.4	115.5	115.4	115.7	114.4	115.0	115.3	116.8	116.0			
Mode (calculated)	118.0	116.9	115.0	115.5	114.8	113.1	113.6	114.3	111.0	112.8	112.7	114.0	114.6			
Coefficient of variation	9.2	9.1	9.4	8.9	8.8	8.7	9.2	9.5	8.4	9.0	9.4	9.2	9.2			
Measure of skewness	0.0	0.11	0.25	0.17	0.23	0.36	0.25	0.19	0.52	0.31	0.35	0.39	0.25			
Percentage over 130 mm	16	14	13	11	11	11	12	9	11	11	11	17	13			
Percentage over 140 mm	1.6	3.0	2.8	2.4	2.5	1.8	1.8	3.6	1.3	2.0	1.6	4.7	2.7			



of ten on the scale, but mainly because there was a large difference between the yearly averages in 1918 and 1919. Thus the arithmetical mean (average) for the 1918 men between the ages of 17 and 19 inclusive was 122 mm, for the 1919 men it was 131 mm. Naturally, it was highly desirable to see which of these two averages was the more nearly correct, and the only way in which this could be done was to secure more data. It was feared also that the sampling from the male community had been affected in some way by the war which drew on the physically fit and left the unfit.

In an attempt to clear up this problem and to obtain accurate standards of blood pressure, we have secured data on 3,070 more men and 3,127 more women—freshmen entering during 1920 and

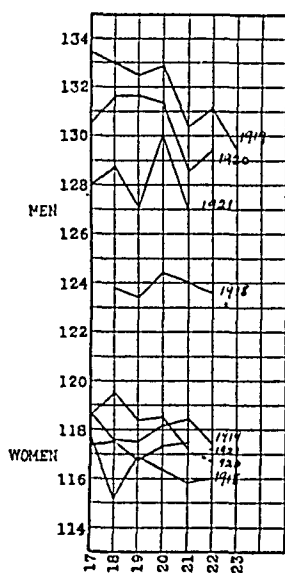


Fig 1—Averages of data on blood pressure in university freshmen secured during the years 1918 to 1921

1921. We now have figures on 6,000 men and 8,934 women, or 14,934 in all. Their distribution is shown in detail in Tables 1 and 2.<sup>3</sup>

3 The averages have been obtained with the help of a short cut method described by Rugg (*Statistical Methods Applied to Education*, Cambridge, Mass., Houghton, Mifflin Co., 1917). As this method is based on the assumption that the data are evenly distributed in each group of five figures (85-89, 90-94, etc.), the results obtained vary a little from those given in the previous paper. Those were based on the individual figures which, as we have noted above, were grouped largely around the multiples of ten on the scale. If the examiners had been more careful in avoiding this tendency, the data would have been distributed evenly, and the averages would probably have been very close to those we have now obtained.

The palpatory method was used in taking the pressures. The men take a tepid shower before the examination, and are examined in the reclining position. They are more likely to stand around in negligee and get cold than are the women. The women's pressures are taken standing. One large aneroid and three mercury instruments were used.

DIFFERENCES IN THE AVERAGES FOR FOUR DIFFERENT  
COLLEGE YEARS

The arithmetical means or "averages" for the data secured year by year have been plotted in Figure 1. As averages based on data from groups smaller than 100 have large possibilities of error, they have been omitted from the graphs. The figure shows the close agreement of the four sets of data from the women, nearly all of which fall within the limits of error determined by the sizes of the groups. We see also the wide divergence of the averages for the men, wider than we would expect from the limitations of the method and the smallness of the groups. (The "probable error" for these averages is actually about  $\pm 0.6$  mm.) The 1918 averages are in a class somewhat by themselves, but it will be noted that the average pressure has fallen steadily since 1919, so that the figures for 1921 are not much above those of 1918. The possible significance of these findings will be discussed later.

## MEASURES OF CENTRAL TENDENCY

Let us now turn back again to Tables 1 and 2 to see what we are going to do with the figures recorded there. They range from 85 to 219 mm. for the men, and from 80 to 189 mm. for the women. The first question that will arise in the mind of a practicing physician is: What are the dividing lines between normal and abnormal? What should be the blood pressure of a healthy young man or woman? Ordinarily, we take the average of all the data as the central point of normality, but it can easily be seen that in the usual mixture of normal and diseased people, there should really be two averages—one for the healthy and one for the diseased. If we average the two groups together, we get a figure which is too high for the normals and too low for the diseased. In this study we see that a number of the averages for the 1919 men exceed 130 mm., and yet, clinically, we know that pressures above 130 in young men are very likely to be accompanied sooner or later by symptoms of hypertension or mild cardiovascular-renal disease. Hence, in this case, we can hardly use the arithmetical mean as a standard of normality.

The median is another figure expressing central tendency. It represents the middle number in the series, on either side of which lie 50 per cent of the data. It is not influenced quite so much by groups of data at the two ends of the distribution, but it still is affected by them a good deal.

In many ways the mode seems to be the most suitable measure for our purposes. It is the value on the scale which occurs most frequently and typically, hence, it forms the apex of the distribution curve (Fig. 2). In a perfectly symmetrical curve it coincides with

the mean and the median, but when the curve is "skewed" the mode remains behind while the mean is pulled over by the large number of data from those persons who are abnormal. The mode can be determined roughly by inspection of the "smoothed" distribution curves, or it may be calculated by Pearson's method<sup>4</sup>. The modes charted in

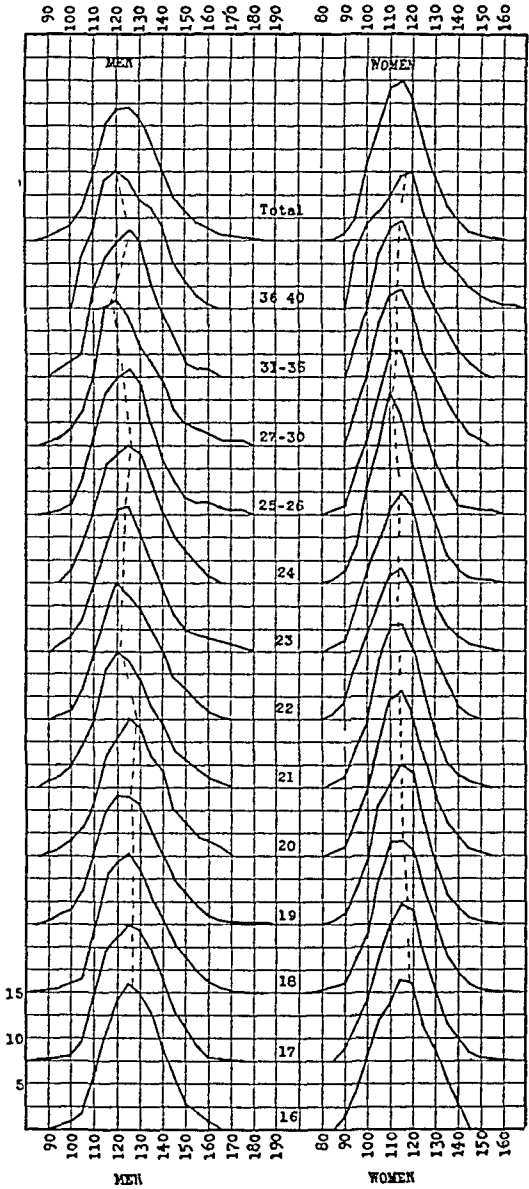


Fig 2—Blood pressure in university freshmen

4 It is hard to know, in writing a paper like this, how far to go in the matter of explaining the terms and methods used in statistical work. Naturally, in the space of a short article, nothing adequate can be given, and the reader who remains puzzled must be asked to turn to the books by Rugg, Whipple (*Vital Statistics*, New York, John Wiley & Sons, 1919) or Thorndike (*Introduction to the Theory of Mental and Social Measurements*, New York, 1916). It is unfortunate that few research workers in medicine are ever given that training in statistical methods which would enable them to analyze and to evaluate quickly and correctly the data with which they are constantly dealing.

Figures 2 and 3 have been calculated, and it will be seen that they correspond pretty closely with the peaks of the curves

It is clear from Figure 3 that the mode for the men drops from 127 mm at the age of 16, to 118 mm at the age of 30. The mode for the women drops from 118 mm at the age of 16, to 111 mm at the age of 24, and after that rises quite rapidly. The mode for all the men was 124.7 mm, and for all the women, was 114.6 mm. These figures, we believe, represent the best standards of normal now available. Unfortunately they represent almost the only standards, because, as pointed out in the previous article,<sup>1</sup> most of the figures published hitherto have been obtained from the study of picked groups of accepted insurance applicants or accepted recruits. Very few attempts have been made to

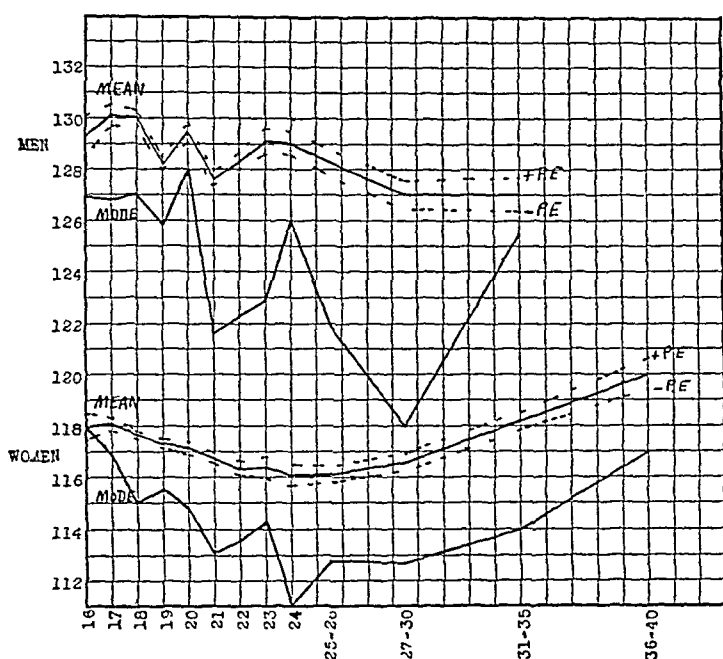


Fig 3—Mode and mean blood pressure in university freshmen

get a fair sampling from the community as a whole. As was argued in the preceding paper,<sup>1</sup> the students in a free university probably represent a good sampling from at least the more intelligent part of the community.

The mean for the women drops very definitely from the age of 17 to 25, and for the men, there is a similar but more uneven drop from 17 to 35. This drop is not quite so marked as that which we have just noted in the curves for the mode.

#### IRREGULARITIES IN THE CURVES

It is hard to understand why the curves for the mean and the mode of the men should be so irregular in places. As will be seen from the location of the dotted lines, which represent the limits of the probable

error of the mean, the deflections about the age of 20 exceed that error, and, in fact, they almost exceed  $\pm 3$  times the standard deviation of the mean. As that range should include 99.73 per cent of the data in a distribution curve, the chances are 9,973 to 27, or 368 to 1, that these deflections are not due to accident but that they mean something. This conviction is strengthened when we turn to Figure 1 where we see that the rise from ages 19 to 20 is found on three out of four of the

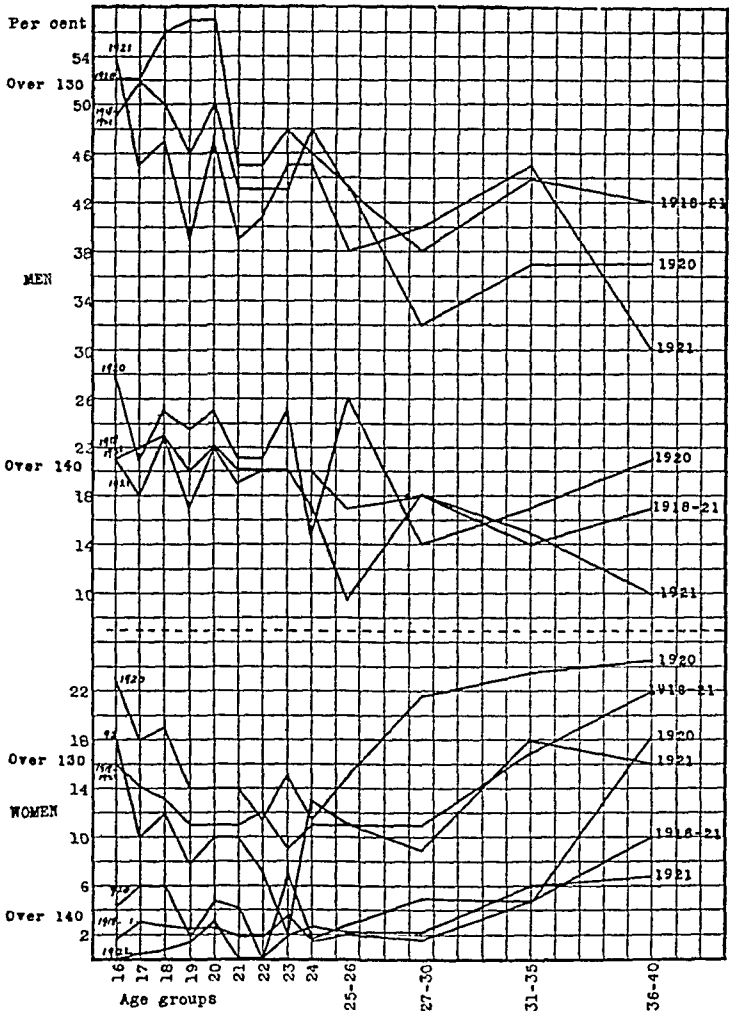


Fig 4—Percentage of blood pressure above 130 and 140 mm

yearly graphs, and the drop from 20 to 21 is definite in all of them. It is strengthened, also, when we note that there are corresponding upward swings in the graph for the mode, and in Figure 2, there are corresponding shifts to the right of the distribution curves.

It would seem, then, that during these years there must be some rhythmic upward tendency in the mechanism which regulates blood pressure. The hard thing to understand is how enough of these yearly tendencies can be in step to affect the curves, because we know that in children there often are big differences between the calendar age and

the developmental age. Such differences in these youths might permit the appearance of broad, rounded rises like the rise in the curve for the men about the ages of 23 and 24, but it is hard to see how they could permit the appearance of a sharp rise like that at the age of 20. Any overlapping of ups and downs would tend to produce a straight line at that point. It is interesting that the women's curves for mean and mode show slight upward tendencies between 19 and 20 and at 23, which, perhaps, correspond to those of the men. These peculiarities, naturally, can be given significance only if they appear again in the same places in curves drawn from data secured by other workers. For the present, they can serve only to make us ask questions.

#### PERCENTAGE OF HYPERTENSION

Figure 4, showing the percentage of the data above 130 and 140 mm is interesting as it shows the peculiar yearly variations, and also the

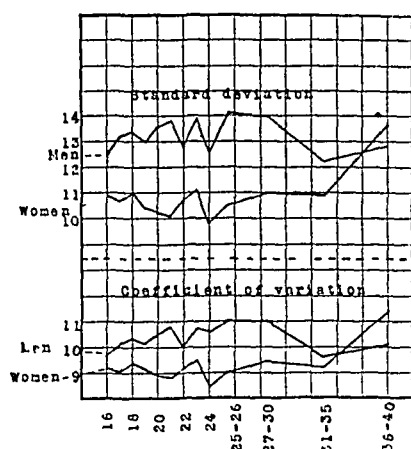


Fig 5—Changes according to age

same general tendencies from the ages of 16 to 40 that we have noted in the curves for the mean and mode. As was pointed out in the previous paper,<sup>1</sup> most writers are agreed that a pressure exceeding 140 in a young person is abnormal, and some are coming to the point where they are willing to place the limits at 130 mm. Here we find from 18 to 26 per cent of the boys with pressures exceeding 140, and from 35 to 57 per cent with pressures exceeding 130 mm. Among the younger women, about 3 per cent have pressures exceeding 140, and 21 per cent have pressures exceeding 130 mm. The remarkable thing is the steady decrease in the incidence of hypertension in the men as they grow older. The question arises: Do their individual pressures decrease, or do many of those persons with high pressures in boyhood drop by the wayside as they grow older? That can only be answered by watching a number of these men for a long period of time.

## MEASURES OF VARIABILITY

Figure 5 shows the yearly changes in the standard deviation and in the coefficient of variation. The standard deviation is the square root of the average of the squares of the deviations from the average of the whole distribution. It is a valuable measure of the variability, and naturally is greater here for the men than for the women. It is interesting to note that the women's pressures are more variable than the men's after the age of 38 or 40.

The coefficient of variation is another measure of the variability, and its graph is naturally very similar to that of the standard deviation. It represents a ratio between the standard deviation and the average from which the deviations were taken.

The measure of skewness which will be noted in Tables 1 and 2 is the one suggested by Pearson. It is obtained by dividing the difference between the mean and the mode by the standard deviation. In both men and women it increases from 16 to 30, after which, perhaps on account of the smallness of the groups, it varies widely up and down.

## DISCUSSION

Unfortunately, the first object of this paper, that of establishing normal standards of blood pressure for young men, has not been accomplished to our entire satisfaction. The new data still show a lack of homogeneity which is disturbing. In attempting to explain these big differences in the measurements made in the four years from 1918 to 1921, we might blame the instruments, the examiners, the sampling, the war, and, perhaps, the influenza epidemic. Errors due to the instruments can probably be excluded as three out of four were mercury manometers and the aneroid was checked from time to time. Furthermore, instruments were exchanged back and forth with the women's department where no such wide variations were observed. Similarly, we can probably exclude errors due to differences in the personal equations of the examiners in the different years. Each year the examining staff consisted of four men and from five to seven women. Of the men, only one remained during the four years, usually there were two hold-overs and two new workers. Among the women, in 1919 there were two hold-overs and three new workers, in 1920 there were four hold-overs and one new worker, and in 1921 there were three hold-overs and four new workers. Any individual differences which may have existed in the readings of the women examiners must have balanced one another because we have seen that the data secured by them year by year are quite uniform. The presumption is, then, that the personal equations of the men also should have balanced one another so as to have become negligible.

The next question is Was the sampling affected by the war? In the previous paper it was assumed that the drafting away of the physically fit into the army and navy might have left behind a larger percentage of militarily unfit who might, presumably, have shown a larger incidence of hypertension. On looking up the figures in the recorder's office we find, however, that the men had already gotten back in large numbers in the college year of 1918-1919 (Table 3). Furthermore, most of the freshmen were under draft age. It is hard to say, therefore, just how the war affected the pressures if it did so at all.

TABLE 3—*Men Entering the University of California in 1915 to 1921, Inclusive*

	Number
1915-16	914
1916-17	1,019
1917-18	847
1918-19	1,531
1919-20	1,782
1920-21	1,571
1921-22	1,364

The strange thing is that the pressures should be so low in 1918, that they should take a big jump in 1919, and should then gradually return in 1920 and 1921 toward the original figures. The fact that the women's pressures follow a rather similar course suggests strongly that we have here a manifestation of some influence affecting both men and women during these years (Table 4). There immediately comes to mind the suggestion that the influenza epidemic which must

TABLE 4—*Blood Pressure Averages for the Data Collected Year by Year*

	Men	Women
1918	123.9	116.3
1919	131.8	118.0
1920	130.6	118.5
1921	128.1	117.3

have attacked many of those registering in 1918-1919, could easily account for the low pressures obtained in that year. It is not so easy, however, to explain the big rise in the following two years. Another solution of the problem would be to say that there are yearly variations in the average human blood pressure, and that a low ebb in 1918 predisposed us to a serious epidemic. Naturally, with only four years' data to go on, and other possible explanations for the discrepancies in sight, this solution cannot be taken seriously, but it might be kept in mind by those who have opportunity to gather similar data in the future.

Another disturbing observation is that the averages even for the 1918 men are considerably higher than those obtained on several hundred



high school boys of corresponding ages in San Francisco. The averages for the high school girls are practically the same as those for the college women. However, as will be seen from Table 5, the range for the boys is much greater than that for the girls, and it increases steadily from the age of 14 to the age of 16. The standard deviation for the 16 year old girls was 9.3 mm. and for the 16 year old boys it was 12.9 mm. These figures agree closely with those obtained at the University. Moreover, it will be noted that hypertension is found commonly among the school boys. One of us (WCA) checked a number of the readings on these boys and found them correct.

#### HIGH BLOOD PRESSURE AND SEX

The study of the new 1920 and 1921 data amply confirms the conclusions drawn in the previous paper. Certainly it would seem that

TABLE 5—*Blood Pressures of High School Boys and Girls in San Francisco*

Pressures	Boys Aged			Girls Aged		
	14	15	16	14	15	16
85-89						1
90-94	4	2			1	
95-99	6	7	4		2	
100-104	11	18	6	3	7	9
105-109	13	12	14	3	9	11
110-114	19	21	19	6	17	10
115-119	10	18	17	7	15	15
120-124	15	18	30	15	36	26
125-129	4	11	11	10	20	19
130-134	4	14	13	5	11	7
135-139	4	6	5	4	10	6
140-144	3	7	7			1
145-149		1	1		1	
150-154		5	3			
155-159			1			
160-164			1			
165-169						
170-174						1
Total	93	140	132	53	129	106
Mean	110.2	118.6	121.2	121.2	120.4	119.8

high blood pressure can hardly be due, as many have thought, to focal infections or to the strenuous life. Otherwise there could not be such marked sexual differences and so high an incidence in youth. Unfortunately, these data do not extend quite far enough to take in the periods of puberty and the menopause. It is highly desirable that such data be secured, because undoubtedly they will throw much light on the nature of high blood pressure.

Since the previous paper was published there has appeared an article by Faber and James on the blood pressures in normal children.<sup>5</sup> Unfortunately, they studied only 651 boys and 450 girls so that the age groups are too small for accurate work. They found the average

<sup>5</sup> Faber and James. *Am J Dis Child* 22:7 (July) 1921.

systolic pressure about the same for boys and girls, rising from 89 mm at the age of 3, to 115 mm at the age of 16. They found a greater variability among the girls than among the boys, which is just the reverse of what is found after 16. They noticed a marked variability in the diastolic pressures of the girls after 13, a change which was not present among the boys. Similarly, Burlage<sup>6</sup> found, in studying 1,700 girls and young women, a rapid rise in the systolic pressure from 104 mm at 9 years to 124 mm at 14 and 15. Then there was a rapid fall to about 114 at the age of 18. After that the pressures were quite constant up to 26 years. Although he used the auscultation method his results agree fairly well with ours.

It is interesting to note that the influence of sex is hardly recognizable in childhood, that it becomes exaggerated about the age of puberty and again in women about the menopause. It is suggestive also that in young women there seems to be a high degree of correlation between the incidence of hypertension and the presence of the various symptoms and signs of ovarian hypofunction. It would seem that the internal secretion of the ovary is able in some way to suppress the tendency to hypertension which many of the girls presumably inherit equally with the men.

This point may, perhaps, be made clearer if we turn to some experimental work done recently on fowls. Goodale<sup>7</sup> showed several years ago that in ducks and hens the extirpation of the ovaries will lead to the assumption by the female of a male type of plumage. Apparently, some substance secreted by the ovary is able to restrain or suppress the male characteristics, and the work of Boring, Pearl and Morgan<sup>8</sup> suggests strongly that it arises in the luteal or yellow pigment containing cells of that organ. Such cells have not been found in the testicles of adult fowls, except in the case of the Seabright bantam and some Campines, where the males are so hen feathered that they are hard to tell from the females. As was to be expected from the theory, when these males were castrated, they developed plumage resembling that of the males of other breeds. The ordinary male fowls, when castrated, retain a male type of feathering.

It has been known for many years that old hens, or hens with diseased ovaries will often develop male characteristics, and similarly, women with undeveloped or diseased ovaries not infrequently show a male distribution of body hair on the abdomen, breasts, and face. It is suggestive that the giving of corpus luteum to many of these women seems to have a restraining influence on the development of their hyper-

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6 Burlage *Proc Soc Exper Biol & Med* **19** 247, 1922

7 Goodale *Biol Bull* **20** 35, 1910, *Amer Naturalist* **47** 159, 1913

8 Boring and Pearl *Anat Rec* **13** 253, 1917. Pearl and Boring, *Am J Anat* **23** 1, 1918. Boring and Morgan *J Gen Physiol* **1** 127, 1919

tention If our reasoning is at all correct, it might be worth while to try ovarian extracts also on men with high blood pressure Another suggestion comes from the work of Torrey and Horning<sup>9</sup> who found that the giving of dried thyroid to normal male Rhode Island Red chicks causes them to develop hen feathering As this does not take place in castrated males, the assumption is that the thyroid extract probably stimulated the function of the few luteal cells which are known to be present in the testicles of very young males

#### SUMMARY

An analysis has been made of the systolic blood pressures of 6,000 men and 8,934 women—freshmen entering the University of California

The pressures of the women are more uniform than those of the men, and they average 11 mm lower

Hypertension is very common among the younger men, about 45 per cent having pressures exceeding 130, and 22 per cent having pressures exceeding 140 mm Among the women, about 12 per cent had pressures exceeding 130, and about 2 per cent had pressures exceeding 140 mm Strange to say, the average pressure for both men and women drops gradually during the first years of adult life

The pressures for the men are grouped mainly about 127 mm at the age of 16, and about 118 mm at the age of 30

The pressures for the women are grouped about 118 mm at the age of 16, about 111 mm at 24, and about 117 mm at 40

Hypertension cannot be ascribed regularly to infections or to the strenuous life It seems to be an inherited peculiarity the appearance of which can be suppressed in women so long as the ovaries function well

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9 Torrey and Horning Proc Soc Exper Biol & Med 19 275, 1922

# BLOOD CONCENTRATION CHANGES IN EXTENSIVE SUPERFICIAL BURNS, AND THEIR SIGNIFI- CANCE FOR SYSTEMIC TREATMENT \*

FRANK P UNDERHILL, PH D,  
GEORGE L CARRINGTON, MD, ROBERT KAPSINOW, MD,  
AND  
GEORGE T PACK, MD

With the cooperation of

EPHRAIM SHORR, MD, HENRY B ROLLINS, MD,  
FLORENCE I PETERMAN, BS, AND ALICE DIMICK, MS

NEW HAVEN, CONN

In extensive superficial burns involving considerable areas of the body's surface a rapid concentration of the blood occurs, and in our opinion this hitherto unconsidered factor is of the greatest importance in the development of the syndrome characteristic of burns. Concentrated blood is a factor which cannot well be left out of consideration in the study of any diseased condition in which it manifests itself. Marked concentration of the blood means a failing circulation, an inefficient oxygen carrier, oxygen starvation of the tissues, fall of temperature, and finally, suspension of vital activities. This viewpoint was initiated during the World War by the results of an extensive investigation of the action of the lethal war gases<sup>1</sup> which produce a noteworthy concentration of the blood as a result of the acute massive edema. Similar conditions obtain in certain cases of influenza<sup>2</sup>.

On first consideration it may be difficult to correlate reactions in burns to those in war gas poisoning in such a manner that one underlying principle can be held responsible for the same ultimate condition in such widely differing abnormal states. Further reflection, however, will lead to the conception that in both pathologic conditions under discussion one fundamental fact stands out clearly—namely, that either detrimental agency leads to an extreme inflammatory reaction and destruction of tissue. This inflammatory reaction, whether in the case of war gas poisoning or in that of extensive superficial burns, meets a response on the part of the body. Fluid is poured out on the surface of the injured area. Up to a certain point the greater and more acute the inflammatory reaction the greater or more rapid will be the response. The acute edema of the lungs in war gas poisoning and in certain types

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\* From the Department of Pharmacology and Toxicology, Yale University, and the Section of Surgery, School of Medicine, Yale University.

1 Underhill. The Lethal War Gases, Yale University Press, 1920, Harvey Lectures, 1917-1919.

2 Underhill and Ringer. J A M A 75 1531 (Dec 4) 1920.

of influenza is readily explained in this manner. An extensive experience with burn cases enables us to assert that a similar rapid pouring out of fluid on the surface of the body occurs, or if the skin is intact the part affected becomes edematous with extreme celerity. The rapid and continued loss of fluid from the blood in burn cases quickly induces a marked concentration of the blood which becomes a factor of prime significance in the fate of the person concerned. It will readily be understood, of course, that other factors than blood concentration have their part in determining the outcome of superficial burns. Nevertheless, we are of the opinion that blood concentration is of extreme importance in any consideration relative to extensive superficial burns. It is a factor which contributes directly to the ultimate fate of the person suffering the injury.

The extent of concentration of the blood compatible with life depends in large measure on the interval during which concentrated blood is maintained. Previous experience would indicate that an animal or man cannot long survive blood concentrated 140 per cent of the normal value. When concentration reaches 125 per cent of the normal value, conditions for the maintenance of life are becoming precarious.

The recognition of blood concentration as a factor of importance leads to a rational method of treatment to control this factor. Rapid and continued introduction of fluid by all possible channels, as by mouth, by rectum, under the skin or intravenously will cause a gradual return of the blood concentration to normal and, in the investigation to be detailed later, a comparable improvement of systemic signs and symptoms. Forcing of fluid is certainly a logical procedure in burn cases, for not only will blood concentration be reduced to a normal level and thus tend to the maintenance of a normal circulation and heart action but any hypothetical poisons will be diluted sufficiently to diminish their degree of toxicity and this dilution will also undoubtedly greatly accelerate their elimination.

The experience with burn cases on which these views are based was gained as a result of observations carried through on twenty-one victims of a local theater fire. These patients were admitted to the surgical wards of the New Haven Hospital and through the courtesy of Dr Samuel C. Harvey, surgeon-in-chief, and his staff, opportunity was afforded us to conduct the investigation. This communication is not concerned with the local treatment of the burned areas but is confined to the general condition and systemic treatment of the patients. It may be stated, however, that, in general, the local treatment consisted of paraffin film dressings with subsequent skin grafting when necessary.

*Methods*—Changes in blood concentration were followed by analyses of the blood for hemoglobin according to the procedure of

Cohen and Smith In the examination of the blood for the determination of nonprotein nitrogen, creatin, creatinin, glucose, urea and chlorids, the system of blood analysis advocated by Folin and Wu was followed

The patients were admitted into the New Haven Hospital in the early evening of Nov 27, 1921, and at once received first aid treatment and were sent to the various wards In most instances some fluid was given at once, but systemic forcing of fluid was not begun until the following day The patients naturally divided themselves into two groups (a) those seriously burned, and (b) those not so seriously burned Fluid was forced by mouth if possible When this could not be done, fluid was introduced per rectum, under the skin, or in one case, in which all other methods failed, it was given intravenously

TABLE 1—*Classification of Burned Cases—Initial Values for Hemoglobin*

Group 1 Seriously Burned			Group 2 Less Seriously Burned		
Case Number	Hemoglobin		Case Number	Hemoglobin	
	In Percentage	In Percentage of Normal		In Percentage	In Percentage of Normal
1	174	(158)	16	129	(117)
2	230	(209)	17	150	(136)
3	200	(181)	18	130	(118)
4	167	(151)	19	129	(117)
5	167	(151)	20	135	(122)
6	167	(151)	21	130	(118)
7	153	(137)			
8	174	(158)			
9	170	(154)			
10	205	(186)			
11	164	(149)			
12	167	(151)			
13	200	(181)			
14	156	(138)			
15	167	(151)			

#### BLOOD CONCENTRATION IN EXTENSIVE SUPERFICIAL BURNS

For obvious reasons extensive observations on these patients were not made at once At 3 p m of the day following the accident, hemoglobin estimations were first systematically carried out and continued for several subsequent days On the basis of the clinical symptoms and the severity of the burns the patients may be divided into two groups, as shown in Table 1

In the table of classification the initial figures for hemoglobin content are given and it is quite apparent that in extensive superficial burns the blood becomes markedly concentrated Moreover, in the division of the more severely burned from those less severely burned there is a corresponding difference in the degree of blood concentration In general, therefore, the more extensively burned patients responded with a greater concentration of the blood

It is of interest to determine the approximate percentage increase of hemoglobin in order to learn the actual gravity of each case on the basis

that an increase of 40 per cent of the normal value is incompatible with life if maintained for an extended period. Such figures may be found in brackets in Table 1. These figures are only approximate since 110 per cent has been chosen as a result of experience for the normal value. Such a procedure is not exact since the normal hemoglobin value varies considerably in different subjects. It is, however, sufficiently accurate for the purpose stated. On this basis it is readily seen that all individuals in Group 1 had a blood concentration above the figure set as a dangerous level. It is also of interest to note that based entirely on clinical symptoms all of these patients, with the possible exception of two (Cases 12 and 14), were at once placed on the danger list. On the other hand, none of the cases in Group 2 were placed on the danger list and only one patient had a blood concentrated to the accepted danger point.

From such data, therefore, it seems conclusive that the determination of blood concentration in extensive superficial burns may serve as an index of the patient's general condition, and will indicate the extent to which fluid should be forced.

#### THE INFLUENCE OF FORCING FLUID ON THE HEMOGLOBIN CONTENT

The systemic treatment of these burn cases consisted simply in the forcing of fluids, water by mouth when possible, and the administration of small quantities of sodium bicarbonate. The quantity of fluid actually taken into the body varied for the individual patients, but, in general, from four to eight liters or more per day were given. In Table 2 may be found figures for hemoglobin during the period of observation, together with the ultimate fate of the case. From these data it may be seen that at first the hemoglobin figures fluctuate considerably, at times the blood concentration even exceeding the initial values. Such a variation may, perhaps, be taken as an indication of the unstable equilibrium of the water balance mechanism. It is quite possible that fluid under conditions of tissue desiccation is employed first of all in resaturating the dried tissues, and that fluid intake under these circumstances will not be evidenced in the blood by altered concentration until a certain water content of the tissues is reached.

Following the period of fluctuation of blood concentration there may be observed a steady fairly rapid fall in hemoglobin content. Coincident with this decrease in blood concentration, improvement in the patients' condition was observed. Those cases (Cases 3 and 10) that ended fatally as a result of the burns terminated either too rapidly for the forcing of fluid (Case 3) or else insufficient fluid was administered to change blood concentration significantly (Case 10). All the other patients recovered from the effects of the burns—although two





deaths occurred later from pneumonia The large percentage of recoveries is noteworthy in view of the severity of the burns suffered by the majority of the patients As a result of our experience we are of the opinion that restoration of blood concentration to a normal level by introduction of fluid is of paramount importance in the systemic treatment of burned cases

In order to bring out more clearly the changes in blood concentration as influenced by fluid administration, graphic illustrations are given in Charts 1, 2 and 3 All these instances were among the most serious cases Inspection of these charts will reveal an apparent relationship between the diminution of blood concentration and fluid intake In

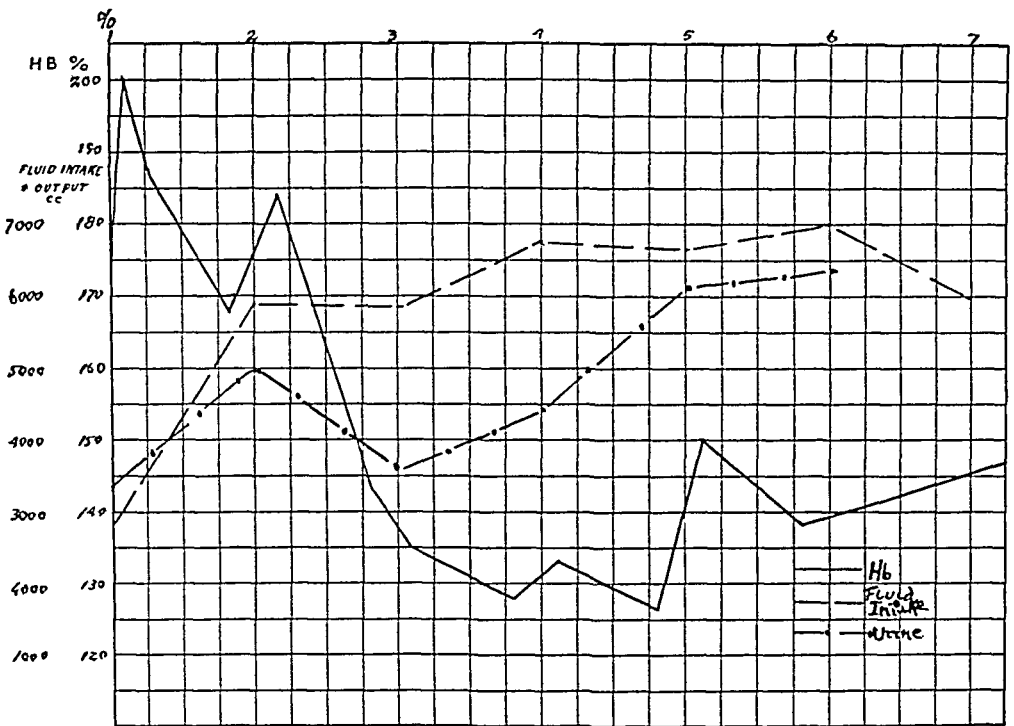


Chart 1—The relation of blood concentration to fluid exchange (Case 8)

general, also, the urinary excretion follows a course similar to the intake but at a considerably lower level Particular attention is called to Chart 3 since in this instance, owing to the impossibility of cooperation on the part of the patient and the failure of introducing sufficient fluid by rectum or subcutaneously, an intravenous infusion of salt solution was given The result is obvious

Although from the figures and other data relative to these observations one is apparently justified in concluding that restoration of blood concentration is of prime significance in burn cases, nevertheless, to the sceptically inclined there are at least two points at which the above conclusions may be attacked In the first place, one may assume that fluid intake has only an inappreciable influence on blood concentration,

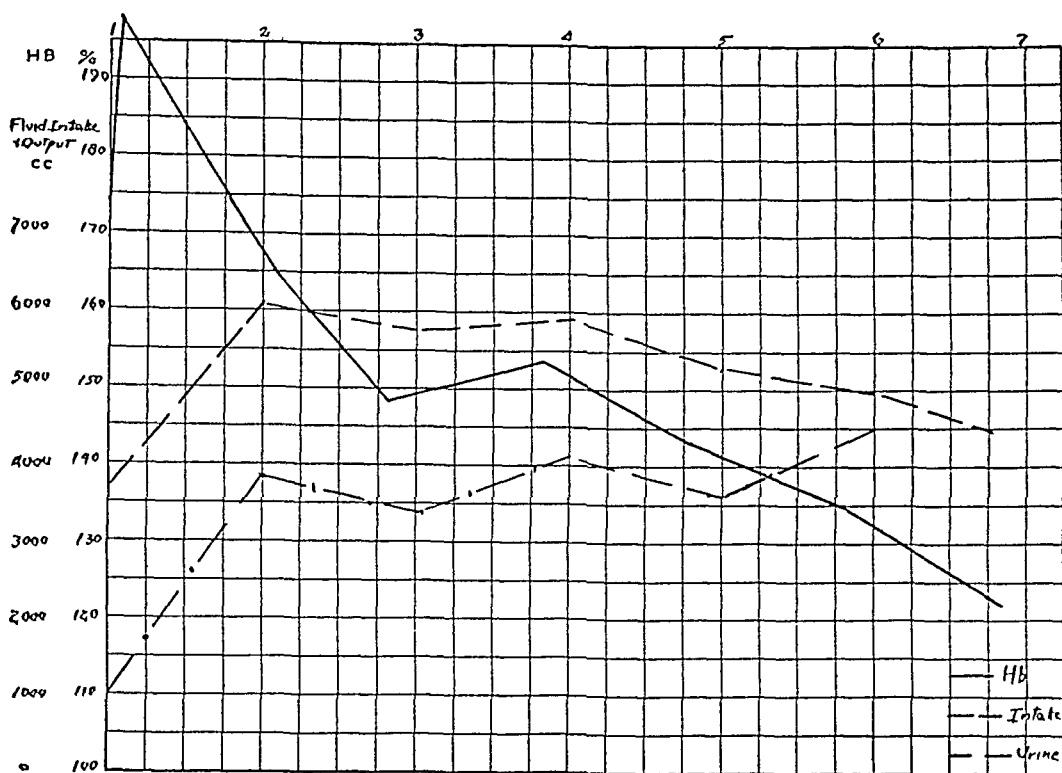


Chart 2—The relation of blood concentration to fluid exchange (Case 1)

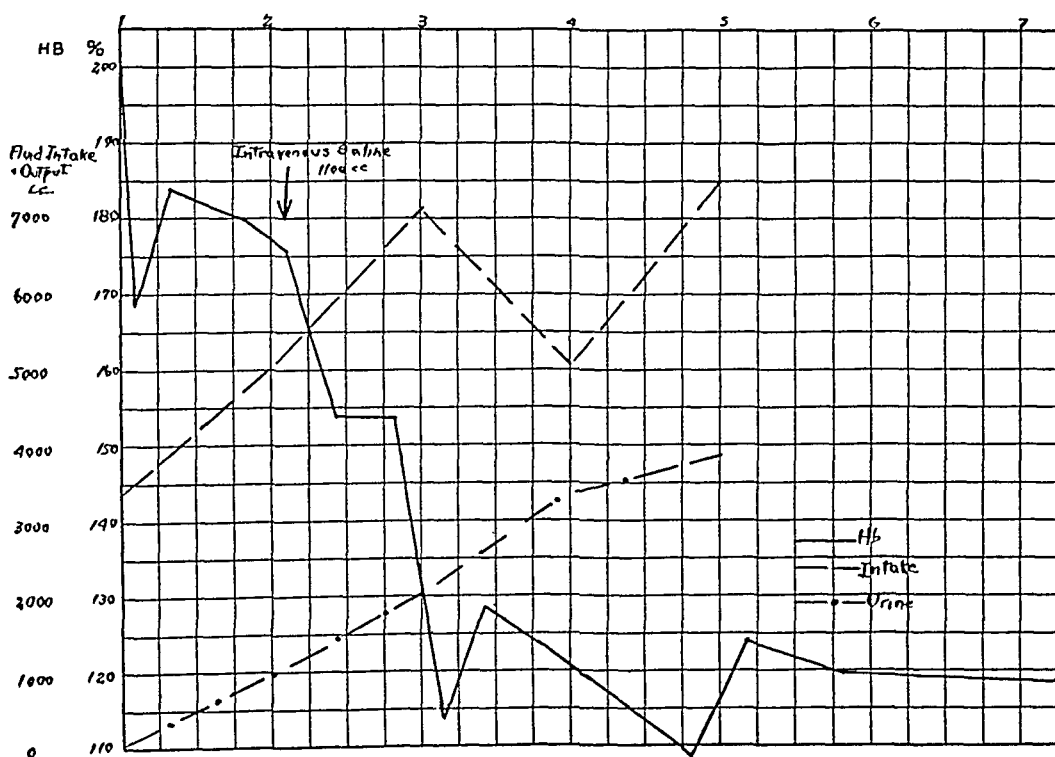


Chart 3—The relation of blood concentration to fluid exchange (Case 13)

that fluid is excreted from the body almost as rapidly as it is ingested. All the available literature on the subject supports such an assumption. One point, however, must be emphasized, namely, that in nearly all instances in which this hypothesis has been put to the test the organism employed was that of a normal person. Herein lies the crux of the whole matter. It is utterly fallacious to predict the behavior toward water administration of an organism suffering from lack of water from observations made on an organism with a sufficiency of water supply. It is quite true that partaking of large volumes of water by normal man or dog does not perceptibly alter the concentration of the blood. So long as the water regulating mechanism of the body is normal such a result is to be expected. On the other hand, when an animal has been deprived of water for a sufficiently long period, blood concentration becomes markedly increased. Water administered under these circumstances causes a rapid fall in the concentration of the blood. The experiments by Keith<sup>3</sup> and by two of us (Underhill and Kapsinow<sup>4</sup>) cause us to reiterate the statement previously made that it is fallacious to draw conclusions relative to the abnormal organism when these inferences are largely based on observations on normal persons, and they furthermore dispose of one of the points of attack cited above.

A second point of attack centers in the query, "Did the fluid intake in these cases actually influence blood concentration or would blood concentration have returned to the normal without such aid?" To answer this question absolutely control experiments would be necessary. Such a control, however, is obviously lacking. The question receives a partial answer from the experiments of Keith and our own cited above together with our experience with war gas poisoning. Death may follow, but blood concentration is not restored to near normal limits under conditions of water lack unless sufficient fluid has been introduced. We believe, however, that the question is fully answered by our experience with one burned patient treated outside the hospital. A victim of the same fire, this patient was cared for at his home by his own physician. Special attention to forcing of fluids was lacking. This case was especially badly burned and presented the typical signs and symptoms characteristic of intoxication from burns, chief among which was an active delirium, it being necessary to take measures to keep the patient in bed. This was succeeded by a period of collapse and unconsciousness, death being anticipated. After a period of eight days, consultation with the physician resulted in the active forcing of fluids. Previous to fluid administration (2 liters of 0.7 per cent sodium chlorid solution subcutaneously) the hemoglobin value was 163 per cent. A few hours after the salt solution had been given the patient regained

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3 Keith. *Am J Physiol* **59** 452, 1922

4 Underhill and Kapsinow. *J Biol Chem*, in press

consciousness, became rational, and was capable of cooperation in taking of fluid. Blood concentration fell rapidly and the patient went on to recovery. The point to be emphasized here is that this patient on the eighth day after being burned still had a blood concentration equal to that in some of our own serious cases on the first day. The presumption is valid that if this patient's blood concentration would have returned to normal of itself it should have done so within a period of eight days, an interval during which none of our own patients maintained such a concentration. A comparison of the influence of water intake on blood concentration at an interval of one day and eight days (the case just discussed) is given in Chart 4.

From such data it would appear that water intake is responsible for the decrease in blood concentration observed in our cases, and it is quite safe to assert that without such water introduction blood concentration would not have taken the decided fall observed in every case. We believe, therefore, that the observations recorded justify the conclusion that water introduction in sufficient quantities to restore blood concentration to within normal limits is of paramount importance in the treatment of burned cases. As a result of this type of treatment, it may be stated that only two patients gave any evidences of symptoms characteristic of intoxication in burns. In these cases unconsciousness at first prevailed, this, however, disappeared after restoration of blood concentration. In all the other cases, the patients presented no untoward symptoms, such as delirium, unconsciousness, gastro-intestinal disturbance, hemoglobinuria, albuminuria, etc. Whether such facts are to be interpreted from the viewpoint that restoration of blood concentration prevented the development of conditions responsible for these symptoms, or that fluid introduction caused prompt elimination of toxic material so diluted as to be innocuous or both, remains a problem the solution of which can be determined only in the future. At any rate, from either viewpoint it would appear that fluid introduction is a rational method of treatment for extensive superficial burns.

#### CHANGES IN THE COMPOSITION OF THE BLOOD

During the first three or four days subsequent to the accident, analysis was made of blood taken from a vein. Particular attention was paid to the estimation of the nonprotein nitrogen fraction on the assumption that if absorption of nitrogenous toxic material occurred the possibility presented itself that an increase in nonprotein nitrogen might be anticipated. From Table 3 it may be seen that changes observable in the composition of the blood during burns vary at most only slightly from the normal limits. Where alterations are above those regarded as normal, the increases noted cannot be interpreted as evidences of absorption of unusual products, but in our opinion they are

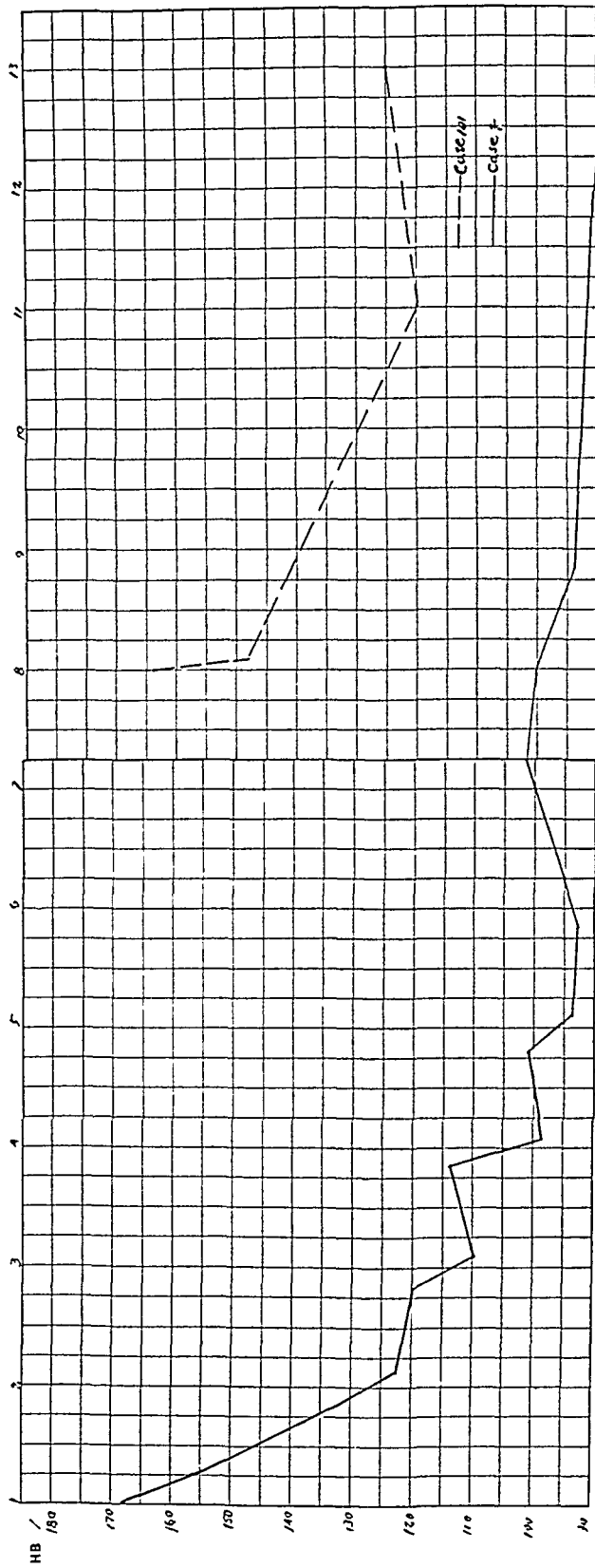


Chart 4.—Comparison of blood concentration changes in one patient (Case 4) receiving early adequate fluid intake and one patient (Case 101) receiving similar treatment eight days later

rather to be regarded as the expression of the change that would be expected in blood highly concentrated. At any rate, until it can be demonstrated that the composition of the blood with respect to the fractions determined here are uninfluenced by concentration of blood to the degree noted in the cases under discussion, we prefer to accept the explanation that blood concentration is responsible for the changes in composition of the blood noted rather than to ascribe these changes to material absorbed from the burned areas.

In one respect the analyses of the blood appended are worthy of comment, namely, in the figures for chlorids. During health chlorids are remarkably constant, varying for whole blood from 0.45 to 0.50 per cent calculated as sodium chlorid. It might, *a priori*, be expected that when rapid interchange of fluid occurs corresponding changes in salt balance would take place since it is to be assumed that when fluid leaves the tissues and blood in response to local inflammatory reactions the fluid poured on the surface is plasma or at least modified plasma. Certain it is that in war gas poisoning in the production of pulmonary edema the fluid entering the lungs has almost the same composition as that of the blood plasma. Moreover, under these circumstances which lead to highly concentrated blood the sodium chlorid of the blood decreases whereas the sodium chlorid of the lungs correspondingly increases. It is quite probable that applying similar reasoning to the process in burns whereby fluid is lost to the burned surface one should expect lowered chlorid content of the blood if the latter has reached a stage in fluid interchange in which normal water balance can no longer be maintained.

Although the figures are in no sense complete, the data on sodium chlorid content of the blood (Table 3) plainly indicate that this salt played a significant rôle in fluid interchange at least during the initial stage of the injury. In general, when blood was highly concentrated, the sodium chlorid content was distinctly low, and when the value for hemoglobin was not so greatly altered, the figures for sodium chlorid approach very closely those of the normal. Expressing it differently, almost without exception the sodium chlorid values were inversely as those for hemoglobin. On this basis the data for sodium chlorid divide the cases into two groups quite as sharply as the hemoglobin figures. It is, of course, quite probable that other constituents of the blood, especially the remaining inorganic components, play a distinct rôle in the water balance of the body. These possible changes were not investigated. It is quite apparent, however, that in the rapid interchange of fluid during the inflammatory stage of burns, sodium chlorid functions prominently. This observation tends to establish the hypothesis that in acute inflammatory processes the mechanism of fluid interchange in response to injury is of similar character whether the irritating agency is war gas or heat.

TABLE 3—Composition of the Blood

Case	Date, 1921	Nonprotein Nitrogen, Mg per 100 C c	Creatinin, Mg per 100 C c	Creatin, Mg per 100 C c	Sugar, Mg per 100 C c	Urea, Mg per 100 C c	Chlorids as NaCl in Percentage
1	Nov 28	38 72	2 23	9 68	166 1	17 90	
	29	34 96	3 26	8 34	177 9		
	30	36 08	2 14	17 65	172 4	16 14	0 37
2	Nov 28	48 12	1 70	11 50	216 4	16 50	
	29	63 60	3 26	9 37	194 2	27 02	0 31
	30	37 00	2 20	7 69	174 8	19 30	0 34
	Dec 1	41 52	2 14	13 10	181 1	20 14	0 43
5	Nov 28	38 52	1 59		133 3		
	29	35 24	2 59	7 60	135 8	15 42	
	30	27 92	1 87	14 29	146 1	15 86	0 37
6	Nov 28	37 48	1 70	12 50	121 6		
	29	36 13	3 26	7 70	97 8	15 30	0 44
	30	33 72	2 14	14 63	181 1	19 68	
7	Nov 28	36 84	1 63	14 28	138 8		0 47
	29	33 76	2 14	15 00	158 7		0 41
	30	31 00	1 92	15 42	149 7	14 80	0 43
8	Nov 28	42 64	1 59	9 20	133 6	9 42	0 44
	29	41 84	3 41	14 63	116 8		
	30	34 92	2 20	16 60	162 3	12 82	0 37
	Dec 1	38 96	1 92	6 20	117 6		
9	Nov 28	36 40	1 78	9 50	117 0	14 32	
	29	33 48	3 00	7 70	99 4	8 72	
	30	30 28	2 02	16 20	128 2	16 72	
	Dec 1	37 24	2 14	12 50	132 9	16 86	0 40
10	Nov 28	55 32	1 74	14 29	199 2	22 98	0 33
	29	50 48	1 97	12 00	181 8	30 16	
11	Nov 28	34 72	1 87	9 23	133 3		0 54
	29	31 64	3 00	7 50	122 5		
	30	31 08	1 97	13 95	181 1	13 06	0 39
	Dec 1	36 72	2 82	12 00	139 6	16 32	0 36
12	Nov 28	38 24	2 27	10 16	173 2	16 24	
	29	39 04	2 59	8 70	120 4	16 26	
	30	38 40	2 20	11 75	138 8	14 08	
13	Nov 29	48 80	2 88	10 55	195 3		
14	Nov 28	31 36	1 66	15 00	131 2	18 18	0 37
	29	33 88	2 34	9 10	98 8	13 82	0 46
	30	27 44	1 87	15 80	150 6	15 00	0 45
15	Nov 28	57 72	2 34		187 9		
	29	67 44	3 57	9 68	146 1	22 08	0 38
	30	40 40	2 14	10 35	134 7	10 44	0 46
16	Nov 28	25 84	1 83	8 82	156 2		
	29	34 36	3 26	7 23	99 8	14 56	
	30	27 44	1 87	15 80	150 6	15 00	0 45
17	Nov 28	30 52	1 87	10 35	110 6	12 02	0 48
18	Nov 28	28 08	1 71	10 16	139 2	13 98	0 50
19	Nov 28	28 16	1 63	9 09	107 8	13 58	
	29	33 48	2 59	8 70	104 8		0 47
	30	33 72	2 08	14 30	128 2	9 94	0 50
20	Nov 28	29 60	1 59	10 00	159 7	13 02	
	29	29 68					

Various estimations of the urinary constituents were also carried through. Owing to the fact that uncertainty exists as to accurate division into twenty-four-hour periods these data are omitted.

#### THE RELATION OF BLOOD CONCENTRATION TO BLOOD PRESSURE AND TEMPERATURE IN EXTENSIVE SUPERFICIAL BURNS

It is well recognized that in extensive superficial burns there may occur a notably low blood pressure which may be accompanied by other clinical signs of a shocklike condition or a state of impending shock. In the analysis of our cases it may be seen (Table 4) that systolic blood pressure in a number of instances is low, and that the pulse pressure is correspondingly diminished. This low pulse pressure coupled with the markedly accelerated heart beat, as indicated by the pulse record, may be taken as an indication of a failing circulation. Such conditions maintained for an extended period are most certain to lead to the clinical picture of shock. Although in the cases of burns under discussion an actual shocklike condition was lacking, it is quite evident that the circulatory disturbances manifested could readily be accepted as indicative of impending shock.

The reason for the rapid onset of circulatory failure in burn cases has not been definitely established. Without discussion of the various viewpoints that have been presented, one factor which may play a rôle is the existence of a highly concentrated blood. There can be no question that a noteworthy fall in pressure under various experimental conditions, as in so-called peptone shock or histamin shock, is accompanied by the rapid development of concentrated blood. The fall in pressure, *per se*, however, can hardly be accepted as the cause for the concentrated blood. On the other hand, a highly concentrated blood may so seriously interfere with the circulatory mechanism that a low blood pressure is the consequence. In gas poisoning, for instance, a shocklike condition may ultimately prevail which is assuredly the result of a failing circulation primarily induced by a blood highly concentrated, in other words, by a decreased blood volume. Applying these facts to our knowledge of the conditions attendant on injury through extensive superficial burns, and noting the similarity in the mechanism leading to circulatory failure, it is not illogical to assume that a highly concentrated blood may be, in large measure, a contributing factor in the development of a shocklike condition, or state bordering on shock. It may be noted, in general, that those cases with the highest initial blood concentration also presented the lowest pulse pressure. On the other hand, some cases showed a low pulse pressure with only a medium blood concentration, and some cases gave evidence of highly concentrated blood with normal pulse pressure. The resistance or sensitive-



TABLE 4—*The Relationship of Blood Concentration to Blood Pressure and Temperature*

Case	Hemo- globin in Per- centage	Fluid Intake, Cc	Pulse	Tempera- ture	Blood Pressure		
					Sys- tolic	Dias- tolic	Pulse Pressure
1 Nov 28	176, 197	3,750	105	103.5	120	65	55
	174, 165	6,090	110	102-104	102	62	40
	149, 153	5,800	100	102-104			
	143, 135	5,980	100	102-104	124	74	50
	122	5,340	100	102-104			
	131	5,000	100	102-103	112	68	44
	135	5,000	100	102			
	127	5,000	95	101-102	128	70	58
2 Nov 28	231, 214, 226	2,000	110	100-101	110	85	25
	195, 214	4,156	100	98.6-102	122	84	38
	156, 135	5,000	100	99.5-102	120	68	52
	126, 131	5,300	100	102-104	134	64	70
	133, 138	5,000	100	104	146	72	70
	134	5,000	100	102-103	136	70	60
	142	5,000	95	101-102	154	82	72
5 Nov 28	167, 161, 155	3,500	95-120	98.4-102	114	75	39
	150, 149	6,500	100-115	99-102	120	62	58
	133, 120	7,476	100-110	101-102	130	68	62
	123, 123	6,400	100	101-102	148	72	76
	112	7,300	100	100-102	142	78	64
	123	7,000	100	100-101	144	84	60
		5,000	95-110	100-101			
	123	5,000	100-110	99-101	154	82	72
6 Nov 28	167, 160	1,200	100-105	101	136	86	50
	153, 144	3,500	95-110	98.6-102	120	74	56
	139, 131	6,570	90-100	99.5-101	132	66	66
	134, 135	7,400	85-100	99-103	128	76	52
	123	6,000	80-100	100-103	124	72	52
	115	6,200	75-100	100-101	138	86	52
		4,500	65-85	99			
	114	4,500	65-75	99	122	70	52
7 Nov 28	153, 150	3,400	80-110	101-104	118	78	40
	167, 183	6,400	90-110	99.5-103	124	72	52
	135, 135	5,500	80-90	99.5-103	128	68	60
	127, 133	4,950	85	99.5-103	122	76	46
	119	6,375	80-95	101.5	124	70	54
	33	6,800	70-90	100	130	78	52
		6,000	80-95	99.5-105.5			
	133	6,000	80-90	100	128	74	54
8 Nov 28	174, 200, 188	2,700	85-100	98-100	140	80	60
	167, 183	5,820	85-105	99-100	136	80	56
	143, 135	5,800	105	99-102	152	78	74
	127, 133	6,700	85-105	102-103	170	86	84
	126, 150	6,600	105	102-104	168	74	94
	139	7,000	100-105	102.5-103.5	156	62	94
	146	6,000	80-90	101.5			
	130	5,000	80-100	100-101	162	72	90
9 Nov 28	170, 174	2,300	90-110	98-101	102	70	32
	165, 156	3,400	110-120	99.5-101.5	120	72	48
	139	?	95-110	101-103			
	135, 135	6,915	100-110	102-104	138	90	48
	125	6,480	100-105	102	124	86	38
	126	6,900	100-105	101.5-102.5	112	78	34
		5,965	90-100	99.5-101			
	144	5,000	80-100	99.5-100.5	120	74	46
11 Nov 28	165, 161	3,760	90-100	101-102	130	80	50
	161, 161	6,580	90-100	101-103	132	80	52
	152, 150	6,600	100-125	103-104	130	78	52
	133, 129	6,160	100-120	102-103	140	72	68
	123	5,520	100	101-103	142	76	66
	125	4,650	90-95	101-103	138	86	52
		5,000	90-100	99-101			
	118	5,000	90-95	99-100	124	82	42
12 Nov 28	167, 167, 169	2,300	60-105	99-100.5	100	68	32
	172, 142	3,900	105-130	99-103	98	64	34
	130, 129	4,700	110-130	102-103	88	58	30
	126, 125	6,340	105-110	102-103	82	48	34
	143	4,450	90-110	102-103	104	64	40
	119	4,100	105-110	102-103	102	52	50
		4,000	90-105	100-102.5			
		4,000	90-105	100-102	110	54	56

TABLE 4—*The Relationship of Blood Concentration to Blood Pressure and Temperature—(Continued)*

Case	Hemo- globin in Per- centage	Fluid Intake, Cc	Pulse	Tempera- ture	Blood Pressure		
					Sys- tolic	Dias- tolic	Pulse Pressure
13 Nov 28	200, 167, 183	3,400	100-130	99-100	90	75	15
	188, 176, 153	5,100	100-125	100-101	80	62	18
	153, 113, 128	7,200	110-120	100-101	110	78	32
	123, 119	5,800	110-115	99 5-101	124	70	54
	109, 123	7,400	110-130	102-103	132	70	62
	120	6,000	95-120	102-103	138	84	54
	119	6,000	95-130	102-104			
14 Nov 28	156, 130	3,900	100-120	100-103	94	66	28
	153, 128	4,300	110-120	100-102 5	102	64	38
	136, 135	4,900	100-125	99-103	98	70	28
	119, 123	5,350	115-125	101-102	108	68	40
	120	5,250	105-120	99 5-102	106	64	42
	114	5,150	105-125	99 5-101 5	98	60	38
		5,000	95-105	98 6-99 6			
		5,000	95-110	98-100	108	62	46
	109						
15 Nov 28	167, 139	900	110-130	98-102	104	84	20
	146, 133	3,790	95-125	101-102	96	78	18
	120, 130	4,650	95-120	101-102 5	96	68	28
	95, 104	4,635	100-110	102-103			
	103	5,800	100-105	102-103	124	64	60
	94	5,550	100-105	101-102			
		5,000	100-110	101-102			
	92	5,000	100	100-101	118	68	50
16 Nov 28	129, 120	3,300	100-105	98 6-100 5	92	65	27
	143, 136	5,050	85-105	99 5-100 5	104	63	61
	126, 131	5,050	95-110	99 5-101	94	68	26
	122, 133	5,400	90-100	99-100	100	64	36
	130	5,050	95-120	98 6-99 5	104	64	40
	136	5,400	95-100	99 0-99 5	96	60	26
	133	5,000	80-130	98 6-99 7			
	126	5,000	95-115	98 6-99 0	96	68	28
	125	5,000	85-100	98 6-99 0			
17 Nov 28	150, 136	2,800	80-90	99 5-100 5	154	108	46
18 Nov 28	134, 114	3,700	90-110	99-100	114	75	39
19 Nov 28	129, 129	4,200	80-95	99-100 5	110	85	25
	127, 138	5,250	90-110	99-102	118	80	38
	139, 142	5,250	100-118	100-101	108	76	32
	129, 130	5,000	105-110	100-101	118	74	44
	120	5,200	95-120	99-100 5	112	70	50
	150	5,400	95-110	99 5-100 5	108	74	34
		5,000	85-100	97 5-99			
	110	5,000	80-90	97 5-99 5	110	68	32
20 Nov 28	135, 120	3,800	105-120	100 5	120	82	38
	122, 125	5,700	100-110	95-101	110	64	46
	128, 113	5,000	70-110	101-102 5	118	60	58
	117, 115	5,000	90-110	99 5-100			

ness of persons to impending shock is well recognized, and dogmatism relative to the degree of blood concentration necessary to produce a failing circulation in any given case is outside the limits of the present discussion

If blood concentration is an important incident in the development of shock in burn cases, it would be logical to assume that treatment designed to restore blood concentration to a normal level should also be beneficial in the restoration to normal of the pulse pressure. In Table 4 it is shown that fluid introduction not only caused the blood to return to a more normal level, but that the blood pressure also improved

to a notable degree. From these data, then, it would appear suggestive at least that fluid intake should improve the circulation by increasing blood pressure. From the observations available, it is indicated that blood concentration may play a distinct rôle in the production of a low blood pressure characteristic of certain burn cases.

The relationship of temperature to blood concentration is close. In war gas poisoning cases temperature changes take place in one of two directions as a result of the degree of blood concentration. With a moderate blood concentration, and with the circulation maintained close to normal limits, the temperature rises above the normal. If blood concentration proceeds to a point at which approximate normal efficiency of the circulation fails, the temperature falls rapidly to a point far below the normal, culminating in death. From experience with gas poisoning cases, the conclusion was drawn "that the temperature is directly related to the efficiency of the circulation, and this, in turn, is determined, in part at least, by the concentration of the blood and the pulse rate." In the observations here discussed the data relative to temperature changes are not so clear cut as obtain with blood pressure. The association of blood concentration with the initial rise in temperature is, however, quite obvious, and it is possible that this increase in temperature may be taken as an expression of the effect of a highly concentrated blood. The later much higher augmented temperature is undoubtedly to be interpreted as a sequence of infection of the injured areas.

#### SUMMARY

In extensive superficial burns the blood becomes highly concentrated. This increased concentration of the blood is regarded as an important factor in the development of many of the clinical signs and symptoms characteristic of burns. The recognition that in extensive burns the blood becomes highly concentrated leads to a rational method of treatment to obviate the untoward symptoms.

Restoration of normal blood concentration by adequate forcing of fluid is accompanied by marked evidences of improvement and the development of the usual sequels (delirium, unconsciousness, gastrointestinal disturbances, albuminuria, hemoglobinuria) of extensive burns is checked. The vast majority of badly burned patients ultimately recover.

Decrease of blood concentration to a point near the normal limits is, therefore, of prime importance in the systemic treatment of burn cases. The determination of the degree of blood concentration may be regarded as an index of the patient's general condition, and will also indicate the extent to which fluid should be forced. The relationship of blood concentration to fluid interchange in inflammatory reactions, with special reference to blood composition and circulatory failure in burns, is discussed by illustrative cases.

REPORT OF CASES<sup>5</sup>

CASE 1—A man, aged 18, a student, who had had measles, mumps, scarlet fever and typhoid, and whose family history was irrelevant, had sustained first and second degree burns of the entire face, hands and ears. Heart and lungs negative.

Treatment<sup>6</sup> consisted of paraffin sprays applied to the burned areas, followed later by skin grafting. No complications arose during convalescence. Recovery was complete.

CASE 2—A man, aged 22, had had typhoid fever. His mother had been treated for tuberculosis. His father died in a fire. The patient had sustained first and second degree burns of the face and hands. The heart and lungs were negative.

Treatment consisted in immersing the hands in boric acid solution. The face was sprayed with paraffin. Skin grafts were applied to the ears and hands. No complications ensued. The patient recovered completely.

CASE 3—A woman, aged 25, a telephone operator, had had influenza three years ago. A slight cough has persisted since. Otherwise her history is negative. The family history is irrelevant. Second degree burns involved the face, eyelids, nose, cheeks, chin, ears, arms, wrist and hands with first and second degree burns of the back, buttocks and the backs of the thighs. The pulse was rapid and of poor quality. The heart and lungs were not examined because of the poor condition of the patient.

Treatment consisted of continuous tub baths. The pulse rose to 160. It was irregular and of poor quality. The woman died twenty hours after admission.

CASE 4—A girl, aged 5, whose personal and family histories were not complete, sustained a second degree burn of the entire face and of both arms to the elbow, and first degree burns of both legs. The heart and lungs were essentially negative, except for a rapid pulse on admission.

Treatment consisted of the use of petrolatum and boric acid ointment dressings. Complications were purulent otitis media and conjunctivitis with hypopyon. Seventeen days after the accident pneumonia developed. Oxygen was administered through a nasal catheter. The patient died twenty-four hours after the development of the pneumonia, on the eighteenth day after the accident.

CASE 5—Man, aged 21, a truck driver, with irrelevant personal and family histories, sustained first and second degree burns of the face, ears and hands. The heart and lungs are negative.

All burned areas were cleaned with boric acid compresses. Later skin grafts were applied. Recovery was complete.

CASE 6—A man, aged 21, a student, who had had mumps, measles and whooping cough, with irrelevant family history, sustained second degree burns of the face and hands. The heart and lungs were negative.

Boric acid ointment was applied to the face. The hands were immersed in boric acid solution. Recovery was complete.

CASE 7—A man, aged 22, a plumber, who had had the usual childhood diseases, and whose family history was irrelevant, presented chiefly first degree burns of the face, neck and hands. The lungs were negative. The heart, except for an occasional extra systole, was negative.

Treatment consisted of the application of continuous wet dressings of boric acid solution, and skin grafts to the ears. Recovery was complete.

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5 The data herein recorded are added for the purpose of showing the extent of the burns. No attempt has been made to give a detailed account of the clinical signs and symptoms.

6 In all cases systemic treatment consisted in the forcing of fluid

CASE 8—A man, aged 18, a student, who had had the usual diseases of childhood, sustained second degree burns of the face, neck and hands. His heart and lungs were negative.

Treatment consisted of constant wet dressings of boric acid solution applied to all burned areas, and the application of skin grafts to the ears and hands. Recovery was complete.

CASE 9—A man, aged 21, a student, had had pneumonia and rheumatic pains in the shoulder and knees. His family history was essentially negative. He sustained second degree burns of the face, neck and ears and first degree burns of the hands and legs. His heart and lungs were negative.

Constant wet dressings of boric acid solution were applied to the burned areas. Skin grafts were applied to both ears. Recovery was complete.

CASE 10—Middle aged man with meager history. First and second degree burns on hands, face, feet and legs.

CASE 11—A man, aged 18, a student, who had had the usual diseases of childhood, and whose family history was essentially negative, sustained first and second degree burns of the face and hands. His heart and lungs were negative.

A paraffin film was applied to the face. The hands were immersed in boric acid solution. Skin grafts were applied to the hands and ears. Recovery was complete.

CASE 12—A woman, aged 47, a housewife, with essentially negative history, sustained first and second degree burns of the face and hands. The heart and lungs were negative.

Picric acid solution was applied to the burned areas. Skin grafts were applied to the hands and ears. Recovery was complete.

CASE 13—A woman, aged 37, a housewife, was admitted in a very serious condition entailed by severe second degree burns of the face and hands, and first degree burns of the chest, back and legs. The patient was very obese. The heart and lungs were not examined.

Paraffin sprays were applied locally. Pneumonia developed seven days later and the woman died.

CASE 14—A woman, aged 24, a housewife, with irrelevant history, sustained first and second degree burns of the face, neck, shoulders, chest and hands.

Paraffin was sprayed locally. Recovery was complete.

CASE 15—A woman, aged 25, a housewife, whose husband was also burned, sustained second and third degree burns of the hands, face and legs. Her heart and lungs were negative.

Picric acid powder was applied to the burned areas. The patient was removed by her private physician to her home for treatment. Recovery was not reported.

CASE 16—A woman, aged 27, a nurse, who had had scarlet fever, sustained first and second degree burns of the hands and face. Her heart and lungs were negative.

Paraffin was applied locally. Recovery was complete.

CASE 17—A woman, aged 63, a housewife, had been treated for high blood pressure. She had had a "shock." Second degree burns of both hands were incurred as well as first degree burns of the nose. A loud systolic aortic murmur was heard. The pulse beat was irregular. Blood pressure was 200/130. The lungs were negative.

Paraffin sprays and boric acid ointment were applied locally. The patient left against advice. Recovery was not reported.

CASE 18—A woman, aged 23, a clerk, had had measles and scarlet fever during childhood. She sustained first and second degree burns of the face and hands. The heart and lungs were negative.

Treatment consisted of paraffin sprays and boric acid ointment applied locally. She left against advice. Recovery was not reported.

CASE 19—A woman, aged 28, a housewife, who had had the usual diseases of childhood, sustained first degree burns of the face, and first and second degree burns of the hands. Her father was burned at the same time.

Treatment consisted of local paraffin sprays. Recovery was complete.

CASE 20—A woman, aged 31, a housewife, who had had the usual diseases of childhood, sustained first and second degree burns of the arms and hands, and first degree burns of the nose and legs. Her heart and lungs were negative.

Treatment consisted of local paraffin sprays. She was discharged to her family physician for further treatment. Recovery was not reported.

CASE 21—A man, aged 18, a printer, who had had the usual diseases of childhood, and whose father died from tuberculosis and the mother from pneumonia, sustained first degree burns of the right cheek. His heart and lungs were negative.

Treatment consisted of the use of boric acid ointment locally. Recovery was complete.

# OBSERVATIONS ON ONE HUNDRED AND NINETY-TWO CONSECUTIVE DAYS OF THE BASAL METABOLISM, FOOD INTAKE, PULSE RATE, AND BODY WEIGHT IN A PATIENT WITH EXOPHTHALMIC GOITER \*

CYRUS C STURGIS, M D

BOSTON

Careful studies during recent years have demonstrated, beyond question, that an elevation of the basal metabolism is a constant finding in the syndrome of exophthalmic goiter. Many careful observations have definitely established this fact and render additional and similar investigation in this direction superfluous. It seems probable, however, that further useful knowledge may be gained by the careful and intensive study of the daily metabolism of persons with exophthalmic goiter over a long period of time. By so doing our information concerning the relationship between the heightened metabolism and this disease may become more accurate and thereby extend the usefulness of basal metabolism determinations in clinical medicine. The present series of observations of the metabolism of a patient with exophthalmic goiter continued over an interval of 202 days, and the determinations were made for the purpose of securing data bearing on the following questions:

- 1 The range of variation in the basal metabolism in exophthalmic goiter on consecutive days
- 2 The relationship between the basal metabolism and the resting pulse, food intake and body weight
- 3 The effect of various types of treatment on the daily basal metabolism

Incidentally, an opportunity was afforded to note the effect of an acute infection on the course of the disease, and to ascertain the influence of the menstrual cycle on the basal metabolism.

## REPORT OF A CASE

*History*—The patient was an Irish woman aged 32 years, who entered the hospital complaining of "nervousness." She had always been strong and healthy, with the exception of rather severe attacks of tonsillitis, which had occurred almost every year. The last attack had occurred two years before. She had been married for thirteen years, and her family consisted of two healthy girls, 12 and 8 years of age. She had always worked hard, caring for her own household entirely alone, and doing laundry work for private families five days out of the week. Her husband had been unable to obtain work for some

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\* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston

time, and this had added to the strain of extra labor which she had been obliged to perform. She had worried considerably about "making both ends meet."

The onset of the present illness occurred about six months before admission, when she noticed that she became unusually tired and nervous at the end of a day's work. She was inclined to be "high strung" and developed emotional instability in the form of frequent attacks of weeping. At this time, she suffered from palpitation and moderate dyspnea on exertion. Her appetite became unusually hearty, yet her weight steadily decreased from 155 pounds (70.3 kg) to 125 pounds (56.7 kg) in six months. She observed a continuous feeling of warmth and an abnormal tendency to perspire. On account of this feeling of warmth, she used few bed clothes and did not dress heavily even in the coldest weather. Her husband had noticed for several months previous to admission that her face had become darker, and that there was a slight puffiness under the eyes. Her condition gradually became worse although she had continued to do her own household duties as well as outside laundry work until the day of admission.

*Physical Examination*—The patient was well developed and nourished. She had the characteristic demeanor and quick movements so often observed in a

TABLE 1—Order of Observations

	Date	Day of Observation
Admitted to hospital	March 1	1st
Acute tonsillitis	From March 13 to March 18	12th to 17th
Forced feeding begun and continued throughout patient's stay in the hospital	March 29	28th
Roentgen ray treatments		
1st	April 15	45th
2d	May 2	62d
3d	May 23	83d
4th	June 13	104th
Ligation of left superior thyroid artery	July 27	142d
Ligation of right superior thyroid artery	July 31	146th
Thyroidectomy attempted, unfavorable reaction toward anesthetization		
Thyroidectomy under local anesthesia	August 16	162d
Discharged from hospital	August 22	168th
	September 19	202d

patient with exophthalmic goiter. Her face had a slightly dark brown tint. There was no outspoken exophthalmos, although the eyes were somewhat prominent. There was a suggestive lid lag. The heart was not enlarged. The pulse was regular, of the collapsing type, and the rate was rapid. There was moderate enlargement of the thyroid gland, which included both lobes and the isthmus. There was a systolic thrill over both lobes, and a systolic and diastolic bruit. The skin was warm and moist. There was marked characteristic tremor of the extended fingers.

*Urine Examination*—Urinalysis revealed albumin, 0, sugar, 0, the sediment showed rare white blood cells, no red blood cells or casts.

*Roentgen-Ray Examination*—The chest was symmetrical with a normal diaphragm. The heart was somewhat enlarged, and the tracheal shadow was somewhat constricted and displaced toward the left side. The lung fields were essentially clear.

In the electrocardiogram, the curves were normal, with the exception of a slight prolongation of the P-R conduction time.

*Course in Hospital*—The patient remained at complete rest in bed in the hospital, with the exception of walking to the toilet once or twice daily. She was permitted to eat all she desired, and a particular attempt was made to furnish her with the articles of diet which appealed to her taste. On March 12, ten days after admission, the patient developed an acute tonsillitis with fever,



which persisted for six days, and at intervals reached 103 F. On March 20, twenty-seven days after admission, a special effort was begun to encourage the patient to eat more food. From that date until April 15, a period of nineteen days, no other treatment than a high caloric diet and rest in bed was given. On April 15, after the patient had been in the hospital for forty-five days, the first roentgen-ray treatment over the thyroid gland was given, and three additional treatments at intervals of approximately three weeks followed. The patient was then observed for a period of forty-four days after the last treatment to determine the result of this therapy. As no change was apparent in the basal metabolism at the end of that time, it was decided that surgery was advisable. Accordingly, on July 27, the left superior thyroid was ligated under procain. On July 31, a similar procedure was performed on the right superior thyroid artery. On August 16, sixteen days after the last ligation, an attempt was made to perform a thyroidectomy, but the patient developed such an alarming reaction, following the administration of the anesthetic, that the operation was abandoned for that day. Six days later, on August 22, the right lobe and about three-fourths of the isthmus were removed under local anesthesia. For several days following the operation the patient was in an extremely precarious condition. Her condition greatly improved, and she left the hospital on September 19, on the two hundred and second day of observation. Her condition subjectively and objectively was improved although the metabolic rate remained elevated, averaging about 25 per cent above normal. Arrangements were made so that she could rest at home and return to the hospital once a week for observation and advice concerning her future care. The chronological sequence of events which occurred during the period of observation of this patient is given in summary in Table 1.

#### METHODS OF STUDY

The patient's metabolism was determined each morning at approximately the same hour (8 30 to 9 a. m.) after a complete fast of from twelve to fourteen hours. The heat production was calculated by indirect calorimetry, and rigid attention to all details was observed in order to make the results as accurate as possible. The expired air was collected by means of a half mask and a modified Tissot spirometer, equipped with suitable valves, for a minimum of two nine minute periods<sup>1</sup>. A different spirometer, mask and valves were used for each period, and duplicate check analyses on the portable

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1 The patient was under continuous observation in the hospital from March 1, 1922, to Sept. 19, 1922, an interval of two hundred and two days, with the exception of six days from June 16 to June 21, inclusive. She was permitted to return home at this time, as she was worried about the care of her children, and it was thought that a short visit to her home would permit her to adjust her household affairs and relieve her mind of this source of anxiety. She remained in bed at home throughout her visit of six days. The patient's metabolism was noted for two full nine-minute periods on each day that she was in the hospital, with the following exceptions. On July 30 and September 4, one period, and on September 19, both periods were lost as a result of technical errors. On August 16, a determination could not be made as the patient was completely anesthetized on that day. On the second and third days following the operation the patient's condition did not permit the metabolism to be determined. On August 22, about two hours after the thyroidectomy, only one six-minute period was obtained, and on August 23, the first post-operative day, the results were calculated from one seven-minute period. Therefore, while the patient remained under observation for two hundred and two days, she was in the hospital only one hundred and ninety-six days, the basal metabolism was determined on one hundred and ninety-two, and two satisfactory nine-minute periods were obtained on one hundred and eighty-eight

Haldane gas-analysis machine were required on each sample of expired air. Outdoor air analyses were performed, at intervals, on each gas analysis apparatus. By such an arrangement, therefore, the metabolism in each period was estimated by a totally different set of apparatus, which obviated the occurrence of an undiscovered error in technic. The adherence to such a procedure, which is somewhat more elaborate than is usually used in clinical metabolism studies, was deemed essential in this work in order to appraise properly the minor changes in metabolism on consecutive days. The basal metabolism, when calculated from single periods, though of value when considered with the clinical data concerning the patient, cannot be regarded as highly accurate.

One hundred and ninety-two basal metabolism determinations were made on this patient. It seems a fair criterion in clinical medicine that the final metabolism result be expressed as the average of two periods which check within 5 per cent<sup>2</sup> of each other. The following is a summary of the 188 metabolism estimations made on this patient, with a statement concerning the accuracy of the result as indicated by the approximation of the two periods. On thirty-eight days, the two periods agreed absolutely, on forty-seven days, they were within 1 per cent of each other, on thirty-five days, they were within 2 per cent, on thirty-two days, within 3 per cent, on eighteen days, within 4 per cent, and on nine days, within 5 per cent. A consideration of the foregoing figures shows that in 81 per cent of the determinations the two periods of each day's determinations were within 3 per cent of each other, while in 94.5 they were within 5 per cent of each other. There were ten determinations wherein the periods varied more than 5 per cent, the differences being as follows: three of 6 per cent, three of 7 per cent, two of 8 per cent, one of 10 per cent, and one of 11 per cent. These differences all occurred either during the first few weeks after the patient's admission, or in the few weeks following the thyroid artery ligations and the lobectomy, both intervals during which the patient's condition was very unstable. From March 20 until August 11, an interval of 134 days, the two periods on each day agreed within 5 per cent.

#### DAILY VARIATION IN BASAL METABOLISM

There is no data in the literature bearing on the daily variation in the basal metabolism on consecutive days in patients with exophthalmic goiter. Benedict<sup>3</sup> has discussed this variation in normal men, and in a series of thirty-five men he found that in periods from five to fifty-three days, in experiments which extended over an interval varying from five days to four years and five months, the minimum and maximum variations were 3.5 per cent and 31.3 per cent, respectively. Benedict and Cathcart,<sup>4</sup> in the course of studies wherein the daily metabolism of a person was determined almost daily from Dec 7, 1911, to Feb 29, 1912, reported that the oxygen consumption varied from a

2 All results of the basal metabolism determinations throughout this paper are expressed in per cent of the average normal according to the standards of DuBois. Hereafter the percentage increase over the average normal is indicated by the figure with a plus sign preceding it.

3 Benedict, Francis G. Factors Affecting Basal Metabolism, *J Biol Chem* 20: 263, 1915.

4 Benedict, Francis G., and Cathcart, Edward P. Muscular Work. A Metabolic Study with Special Reference to the Efficiency of the Human Body as a Machine, Washington, D. C., 1913. Carnegie Institution of Washington.

minimum of 225 c c to a maximum of 262 c c, although the environment and diet of the person remained constant, except on certain days when conditions were admittedly abnormal, and on these the metabolism results were therefore excluded. Benedict concludes that the basal metabolism of a person is a function, first, of the total mass of active protoplasmic tissue, and second, of the stimulus to cellular activity existing at the time the measurement of the metabolism determination is made. The latter, he feels, accounts for the variations in the metabolism of normal persons which occurs from day to day.

In order to obtain an accurate estimate of the variation in the basal metabolism of the patient herein reported, it was necessary to exclude certain days when such abnormal factors as fever and operative procedures were adequate to account for marked changes in the basal metabolism. With the exception of a febrile period of five days, which was associated with an acute tonsillitis, and of several days immediately following the thyroid artery ligations and thyroidectomy, when there was slight fever, the patient's temperature did not exceed 99 F by mouth. The body temperature was carefully determined after the patient came to the laboratory, once just before the first metabolism period and again between the first and second periods. With the elimination of the periods, when obviously abnormal conditions prevailed, there remained the observations on 142 days, on which conclusions may be based.

The greatest fluctuations in the metabolic rate occurred during the patient's first eleven days in the hospital. During this time (Chart 1) the greatest change from one day to the next amounted to 33 per cent, this being the difference between the determinations on the first and second days. This merely emphasized what is already well known but not fully appreciated by many clinicians, that, owing to apprehension, the first metabolism determination on any patient is likely to be higher than subsequent ones. It is interesting to note, however, that in the observations between the tenth and eleventh days after the patient's apprehension had been completely eliminated, there was a change as great as 23 per cent. This clearly illustrates that not only the initial, but some of the early subsequent, metabolism tests may show a change of considerable magnitude, which may easily lead to an incorrect judgment as to the future care of the patient. This is strikingly apparent on considering Chart 1. If only two isolated observations had been made on this patient, one on the first day and one on the eleventh day, the conclusion would have been that the metabolism was falling rapidly, had the two observations been made on the second and tenth days, the conclusion would have been that the metabolism was remaining stationary, had they been made on the eighth and tenth days, the conclusion would have been that the metabolism was rising. Two

observations, therefore, do not indicate in every patient whether the course of the disease is upward, downward or stationary, but more tests must be made which will more nearly form a curve on which to base judgment. A survey of the patient's daily metabolic rate from March 19 to July 26, just before the operative procedures were insti-

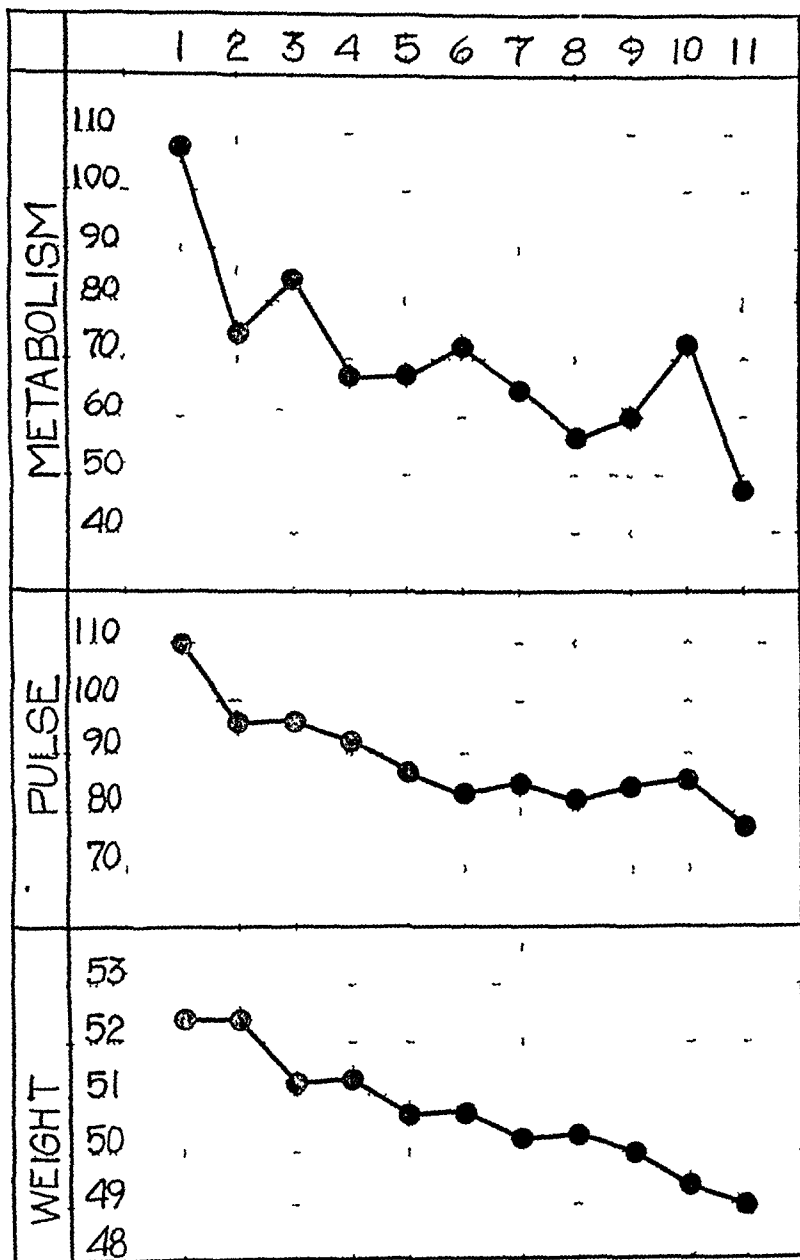


Chart 1—The basal metabolism in per cent of the average normal person, resting pulse rate per minute and body weight in kilograms for the first eleven days in the hospital. Note the difference (34 per cent) between the determinations on the first and second days, and also the difference (23 per cent) between the determinations on the tenth and eleventh days.

tuted, indicates that the patient's condition had become stable. During this interval of 123 days, the level of the basal metabolism remained remarkably constant. In this series of 123 estimations on consecutive

days, the greatest daily difference was 14 per cent. In 80.5 per cent of the determinations, the variations from one day to the next were within 5 per cent of each other, which is considered not above the limit of error, in 96 per cent the variation was within 8 per cent, in only three instances was the daily variation over 10 per cent, these differences were 13, 14 and 11 per cent. The greatest variations often followed a period when the patient was nervous or upset over home conditions, and in a number of instances they followed a more or less sleepless night. It is to be expected that changes in the basal metabolism would occur in a patient with exophthalmic goiter under the influence of nervousness, worry, apprehension or fear, and it seems remarkable that even greater fluctuations did not result from such factors in a patient with a disease which is characterized by marked emotional instability. In rare instances, however, there were changes in the metabolism which could not be accounted for by excitement or other known factors. It is impossible to state whether these fluctuations resulted from variations in the stimulus, which is the cause of the accelerated metabolism in exophthalmic goiter, or whether they were due to slight muscular movements which escaped notice despite the closest observation. These observations emphasize the importance in clinical medicine of a conservative attitude toward the interpretation of single metabolism determinations. A few isolated tests, particularly during the first week or two of the observation period, might easily lead one to an erroneous conclusion concerning the course of the disease. After the patient's condition has become more or less stable, the fluctuations in the metabolism are much less, but even then they may in rare instances amount to as much as 14 per cent from one day to the next.

#### THE RESTING PULSE RATE

A study of the correlation between the resting pulse rate and the basal metabolism in this patient revealed little in addition to what has already been observed. The resting pulse was determined according to the method previously described.<sup>5</sup> Immediately after the patient was brought to the laboratory, the radial pulse rate was counted for a full minute every third minute while the patient was resting quietly in bed. After the pulse rate had become constant, which was usually in one-half hour, the expired air was collected for two nine-minute periods. During these two periods the pulse rate was counted every third minute, and the average of these counts has been taken as the resting pulse rate. It is of interest to note that this patient fell into the rather small group of persons who have an increased metabolism and a relatively

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<sup>5</sup> Sturgis, Cyrus C., and Tompkins, Edna H. A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, *Arch Int Med* 26 467 (Oct) 1920

slow pulse rate The initial metabolism observation was  $+108$ , while her pulse rate at this time was 110 per minute, which is somewhat lower than is ordinarily encountered in association with such high metabolism Thereafter, during a greater part of the patient's stay in the hospital, the pulse rate was usually between 75 and 85 per minute Once the ratio between the basal metabolism and the pulse rate had been established, the latter indicated accurately the changes in the metabolism with few exceptions Read<sup>6</sup> has studied the correlation between the basal metabolic rate and pulse and pulse pressure and has observed that a patient with an increased metabolism and a relatively slow pulse is likely to have a high pulse pressure He is of the opinion, therefore, that a combination of the pulse rate and pulse pressure is a better index of the response of the circulatory system than either one when considered alone It is of interest in this patient that in association with the relatively slow pulse, the pulse pressure was always rather large, fluctuating between 70 and 90 mm of mercury, which is in accord with Read's observations

#### RELATIONSHIP BETWEEN THE FOOD CONSUMPTION, ENERGY EXPENDITURE, AND BODY WEIGHT

Friedrich Muller<sup>7</sup> first called attention to the loss of body weight and nitrogen in patients with exophthalmic goiter, despite the large amount of food consumed, and it was he who first emphasized that this was an indication of an accelerated metabolism It is now well established that the dietary requirements are increased in patients with this disease on account of their increased heat production The combination, therefore, of a large food intake and a loss or failure to gain in body weight, when encountered in the clinical history of a patient, should suggest the possibility that the patient's metabolism is increased The only other common clinical entity which presents these circumstances is diabetes mellitus Patients with an increased metabolism do not always lose weight It may occur that the food consumption is so large that it compensates adequately for the dissipated energy and at the same time provides sufficient calories to permit the deposition of fat and protein in the form of body tissue, with a resultant substantial increase in body weight In order to obtain more accurate data concerning the correlation between the food consumption, body weight and metabolism in patients with hyperthyroidism, a survey was made from the records of this hospital of fifty patients with hyperthyroidism The average basal metabolism of this group was  $+44$

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6 Read, J Marion Correlation of Basal Metabolic Rate with Pulse Rate and Pulse Pressure, *J A M A* 78 1889 (June 17) 1922

7 Muller, Friedrich *Fur Kennt der Basedow's Krankheit*, *Deutsch Arch f klin Med* 51 335, 1893

per cent, the lowest metabolism encountered in the series was + 18 per cent, while the highest was + 86 per cent. Thirty-eight or 76 per cent of these patients gave a history of loss of weight, averaging 26 pounds (11.79 kg), over an average length of time of eleven months. In 68 per cent of the cases, there was a statement in the history that the loss of weight had occurred even though the appetite had been good or abnormally hearty. The combination of an elevated metabolism and a small food intake results inevitably in a marked loss of weight due to the consumption of the person's own tissue in order to supply the caloric requirements. One patient in this group had a poor appetite for eighteen months, and throughout this interval his metabolism remained moderately increased. There was a resultant decrease in body weight from 220 pounds (99.79 kg) to 115 pounds (52.16 kg). The loss, gain or stationary level of the body weight depends on the relationship between two factors: the energy provided in the form of food, and the total amount of energy expended, which is dependent chiefly on the level of the basal metabolism and the amount of muscular activity. One patient of this group gained 50 pounds (22.68 kg) in three months, though he was not resting in bed and regardless of the elevation in his basal metabolism, which was always over + 50 per cent. His appetite during this period was insatiable.

Hirschlaff<sup>8</sup> has reported the most intensive, careful and complete metabolism studies of a patient with exophthalmic goiter. The patient was a girl, aged 21 years, who had the classical symptoms and signs of the disease. For forty-six days the average food consumption in calories was 5,300. It was calculated that food amounting to 360 calories were lost daily in the feces. During the time the patient's weight increased from 41.7 to 53.5 kilograms, a gain of 11.8 kg. This observer calculated that 5.6 kg of this represented "flesh" while 6.2 kg was stored as fat. Boothby<sup>9</sup> studied the food intake and basal metabolism in two patients with hyperthyroidism and decided that the caloric requirements in these patients was about 75 per cent greater than the requirements as calculated from the basal metabolism.

The studies on the patient herein reported are summarized in Table 2. The average daily food intake for each week is shown in grams of protein, fat, carbohydrate and total calories, while the energy expenditure is represented by the column of figures showing the average daily basal metabolism for twenty-four hours. In addition, a column has been included which represents the average basal metabolism per twenty-

8 Hirschlaff, W. *Zur Pathologie und Klinik des Morbus Basedowii*, *Ztschr f klin Med* **36** 200, 1899.

9 Boothby, Walter M., and Sandiford, Irene. *A Preliminary Note on the Food Requirement in Hyperthyroidism*, *Med Clin of N A* **5** 425 (Sept) 1921.

four hours, to which has been added 10 per cent for the specific dynamic action of food, and 15 per cent for additional movements while the patient is in bed. If the assumption as to the amount of calories consumed in the specific dynamic action of food and the movements in bed are correct, the figures in this column should indicate, theoretically, the approximate amount of energy expended by the patient each twenty-four hours. The last column shows the average weight per week in kilograms.

A consideration of Table 2 shows that the daily average food intake for a period of twenty-eight weeks was 3,953 calories per twenty-four hours, while the average daily energy expenditure, according to the method of computation already stated, was 2,349 calories. The differ-

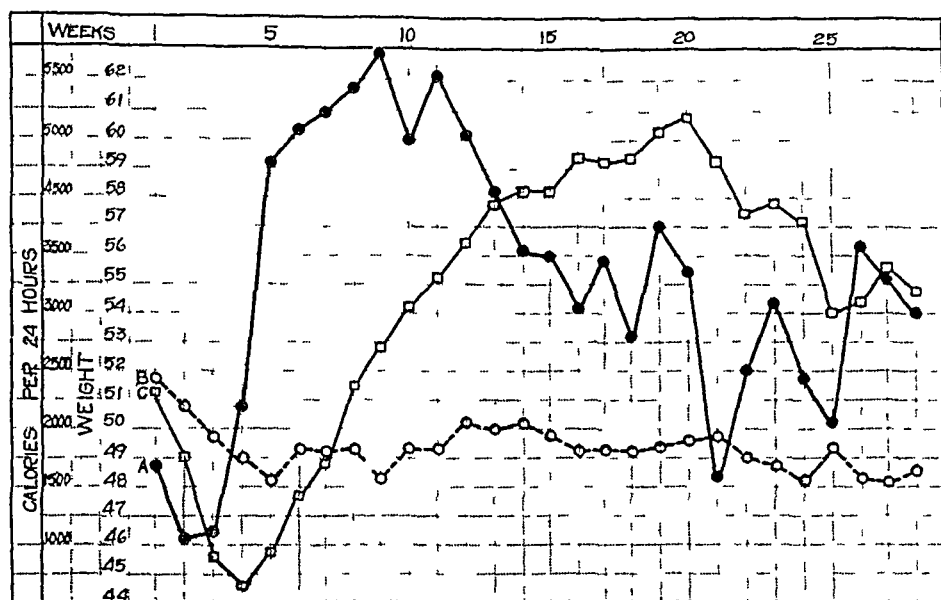


Chart 2—Relationship between the average twenty-four hour caloric intake and expenditure and body weight per week for twenty-eight weeks. A, number of calories in the form of food consumed by the patient, B, energy expenditure per twenty-four hours calculated from the basal metabolism, to which has been added 10 per cent of the total caloric intake for the specific dynamic action of food, and 15 per cent for additional movements while the patient was resting in bed, C, body weight in kilograms. The average weekly energy expenditure remained fairly constant throughout the entire observation period, while the body weight, which varied widely, was directly proportional to the amount of food consumed.

ence between the energy intake and expenditure is, therefore, 1,604 calories, which must be accounted for by (a) food which is not absorbed but is lost in the feces, (b) food which is ingested and absorbed but not burned and, therefore, stored as body fat and protein (c) additional movements which are eliminated during the basal period but are present more or less constantly during the day. Any additional



energy expenditure held to be accounted for under this head, then, would indicate that the original theoretical allowance of 15 per cent for movements while in bed was inadequate

A consideration of the investigations relating to the utilization of food in patients with exophthalmic goiter indicates that as much food is absorbed as in a normal person. The average of the various food constituents found in the stool, as reported by F Muller and Hirschlaft,<sup>10</sup> is as follows: carbohydrate 62 per cent, fat 10.9 per cent and nitrogen 8.1 per cent. Applying these averages to the protein, fat and

TABLE 2—*The Daily Average Food Intake, Basal Metabolism, Estimated Total Energy Expenditure and Body Weight per Week for Twenty-Eight Weeks*

Weeks	Date	Food Intake				Basal Metabolism per 24 Hours	Basal Metabolism per 24 Hours + 25 per Cent *	Body Weight
		Protein	Fat	Carbohydrate	Calories			
1	March 8	76	127	233	2,448	2,311	2,889	51.4
2	15	54	89	132	1,590	2,235	2,723	49.0
3	22	52	89	165	1,717	1,972	2,452	45.6
4	29	87	143	263	2,765	1,776	2,250	44.8
5	April 5	101	350	305	4,920	1,774	2,775	45.7
6	12	106	363	336	5,188	1,851	2,331	47.6
7	19	108	370	295	5,093	1,838	2,297	49.0
8	26	106	379	397	5,587	1,885	2,357	51.5
9	May 3	120	397	422	5,914	1,960	2,110	53.5
10	10	104	353	412	5,399	1,911	2,389	54.9
11	17	105	398	377	5,678	1,897	2,390	55.2
12	24	93	352	406	5,320	2,064	2,580	56.5
13	31	90	326	331	4,758	2,029	2,554	58.0
14	June 7	75	271	326	4,164	2,046	2,558	58.1
15	14	70	279	303	1,124	1,946	2,415	58.1
16	27	70	223	256	3,411	1,865	2,382	59.5
17	July 4	77	255	324	4,016	1,889	2,374	59.4
18	11	80	260	299	3,972	1,862	2,328	59.6
19	18	86	301	325	4,484	1,874	2,343	60.3
20	25	80	244	322	3,917	1,922	2,402	60.9
21	Aug 1	41	124	186	2,084	1,947	2,438	59.5
22	8	43	200	260	3,102	1,766	2,249	57.5
23	15	72	226	321	3,713	1,779	2,227	57.9
24	22	60	193	234	3,000	1,676	2,094	57.2
25	29	41	160	230	2,599	1,865	2,344	54.0
26	Sept 5	89	278	323	4,275	1,637	2,046	54.3
27	12	76	274	288	3,855	1,633	2,028	55.1
28	19	73	231	286	3,620	1,463	2,133	54.8
	Average	80	208	299	3,953	1,882	2,349	54.6

\* Ten per cent added for the specific dynamic action of food, and 15 per cent for additional movements in bed.

carbohydrate intake of this patient, it would indicate that an average of 362 calories, or 9.2 per cent, of the total caloric intake were lost daily in the feces. This seems to be a fair estimate of the average amount of food lost in the stools in patients with exophthalmic goiter who are consuming a high calorie diet, and hence this value, based on the observations of Muller and Hirschlaft, has been used. Another

10 Muller, Friedrich, and Hirschlaft, W, quoted by Magnus-Levy in Von Noorden, C. Metabolism and Practical Medicine, Chicago, W. T. Keener & Co. 3 1000, 1907.

possible source of energy loss, in some patients with this disease, is a glycosuria which may be of importance. In this patient repeated examinations of the urine did not show the presence of sugar. The food which was stored as body tissue is represented in this patient by a gain in weight of 3.4 kg. As glycogen is not stored in an appreciable amount, it is inferred that this gain in body weight must be represented by deposits of fat and protein. As the chemical studies were incomplete in this case, it is impossible to state the exact proportion of these two food elements which were stored. Judging from the studies in Hirschlaff's<sup>8</sup> case, it would be approximately correct to assume that 50 per cent was stored as fat and 50 per cent as protein. A deposition of 1.7 kg of fat and a like amount of protein over a period of twenty-eight weeks would represent a caloric value of 132 calories daily. A summary of the caloric intake and expenditure for the twenty-eight weeks' observation period is presented in Table 3.

TABLE 3—*Summary of Caloric Intake and Energy Expenditure for One Hundred and Ninety-Six Days*

Average daily caloric intake (Protein 80 gm, fat 278 gm, carbohydrate, 200 gm)	3,953
Computed energy expenditure (Basal metabolism plus 25 per cent)	2,349
	1,604
Calories lost in feces daily (estimate)	362
	1,242
Calories stored as fat and protein daily (estimated)	132
	1,110*

\* One thousand one hundred and ten equals 59 per cent of average basal metabolism

As all known sources of energy expenditures have been considered, as indicated in Table 3, it must necessarily be deduced that the balance of 1,110 calories, which constitutes 59.0 per cent of the average daily basal metabolism, must have been consumed in the almost incessant, semipurposeful movements, which are so characteristic of a patient with exophthalmic goiter. It appears, therefore, from the data just submitted that an allowance of 15 per cent for additional movements while in bed is an insufficient amount by 59 per cent of the basal metabolism. In calculating the dietary requirements of a patient with exophthalmic goiter, therefore, it is necessary to add to the basal metabolism, 10 per cent for the specific dynamic action of food, and 74 per cent for movements while at "complete rest" in bed, or a total of 84 per cent. This conclusion is in approximate agreement with the conclusions of Boothby,<sup>9</sup> who suggests that at least 75 per cent be added to the basal metabolism to meet the dietary requirements in this disease.

It is interesting to note the huge quantity of food which these patients are able to consume and apparently utilize. From April 5 to May 31, a period of fifty-six days, the patient's average daily caloric intake

was 5,254 The lowest average daily caloric intake during any one week of this time was 4,777, while the highest was 5,723 During this period the patient's body weight increased from 44.8 kg to 56.5 kg, a gain of 11.7 kg The ingestion of such a large amount of food by a woman varying in weight from 44.8 kg to 56.5 kg and resting in bed, seems all the more remarkable when compared to the calories necessary for a man of 70 kg who is doing hard work, which Voit estimates at 3,574 per twenty-four hours, Rubner at 3,362 per twenty-four hours and Atwater at 4,150 for a similar period <sup>11</sup>

#### IMMEDIATE AND SUBSEQUENT EFFECTS OF AN ACUTE TONSILLITIS

After the patient had remained in the hospital eleven days, at which time the metabolic rate had fallen to 49 per cent above the average normal, an acute attack of tonsillitis developed which manifested itself by fever as high as 103 F, and reddened, swollen tonsils which were covered by a moderate amount of exudate The patient's temperature was elevated from 8 p. m. on March 12 until midnight on March 17, a period of approximately five days The highest temperature during this time was 103 F, and the lowest was 99.8 F, while the average was approximately 101 degrees

The observations on the temperature, metabolism, pulse rate, food intake, and loss of weight during this illness are of interest from two standpoints (1) the immediate effect of an acute infection on a patient with exophthalmic goiter, and (2) the influence of the acute infection on the subsequent course of the thyroid disturbance

*Immediate Effect of an Acute Infection*—It has been observed by DuBois and his co-workers <sup>12</sup> that with an increase in body temperature, the basal metabolism rises, in a definite relationship to the temperature If the temperature remains elevated and the food intake is not increased a proportionate amount, the patient will of course consume his own tissues and lose in body weight This applies also to a patient with exophthalmic goiter, but in this disease the situation is more of a strain on the heat regulating and nutritive systems of the body as the increase in metabolism, which results from fever, is an increment which must be added to an already elevated metabolism due to the preexisting exophthalmic goiter In the patient under observation, the heat production increased sharply from 49 per cent to 104 per cent above normal, as the fever rose from normal to 102.2 F (by mouth) Thereafter for a period of five days the metabolism remained elevated, but maintained a definite relationship to the degree of fever, as shown in Table 4

11 Lusk, Graham The Science of Nutrition, Ed 3, Philadelphia, W B Saunders Company, 1921, p 350

12 DuBois, Eugene F The Basal Metabolism in Fever, J A M A 77 352 (July 30) 1921

With the marked rise in the metabolism associated with the fever, the patient's appetite failed, hence there was a diminution in the caloric intake. From the patient's admission until the onset of the acute tonsillitis (eleven days), the patient's average daily food consumption had been approximately 2,500 calories, and despite this her weight had decreased from 52.6 kg to 49.0 kg, a loss of 3.6 kg. During the five days in which the patient had fever, her food intake diminished to an average of 1,199 calories daily. The patient, therefore, had the undesirable combination of an increased energy expenditure associated with a decreased food intake. The result was a decrease in body weight from 49 kg to 46.4 kg (2.61) in five days. This weight loss, when added to the amount the patient had lost during the eleven days previous to the onset of the acute tonsillitis, amounted to 7.2 kg (approximately 16 pounds) in sixteen days. This illustrates one striking

TABLE 4—*Relationship Between the Body Temperature and the Basal Metabolism*

Day of Month	Temperature (by Mouth) Taken at the Time of the Metabolism Determination	Basal Metabolism per Cent Above Average Normal
March 12	98.0	49
13	102.2	104
14	102.0	91
15	101.4	90
16	100.5	75
17	99.4	65
18	98.6	58

ing and immediate effect of an acute infection in a patient with exophthalmic goiter. Furthermore, an additional strain is thrown on the heat regulatory apparatus of the body, which is obliged to deal with the elimination of a large excess of heat owing to a combination of the increased heat production as a result of the exophthalmic goiter and that due to the fever. This patient during the febrile period seemed very drowsy, suffered greatly from a feeling of warmth and appeared "toxic."

#### INFLUENCES OF THE ACUTE TONSILLITIS ON THE SUBSEQUENT COURSE OF THE THYROID DISTURBANCE

Recently Squire<sup>13</sup> has reported two cases of exophthalmic goiter, in which both patients manifested great improvement subsequent to attacks of acute tonsillitis. The most striking change was the remarkable increase in weight, one of the patients gaining 56 pounds (25.4 kg) and

<sup>13</sup> Squire, Theodore S. Improvement in Graves' Disease Subsequent to Severe Focal Infection, *Am J M Sc* **160** 358, 1920

the other 115 pounds (52.16 kg) in approximately six months. It was thought by this observer that probably the improvement resulted either from invasion of the thyroid gland by infection with subsequent loss of secretory tissue or as a result of glandular exhaustion.

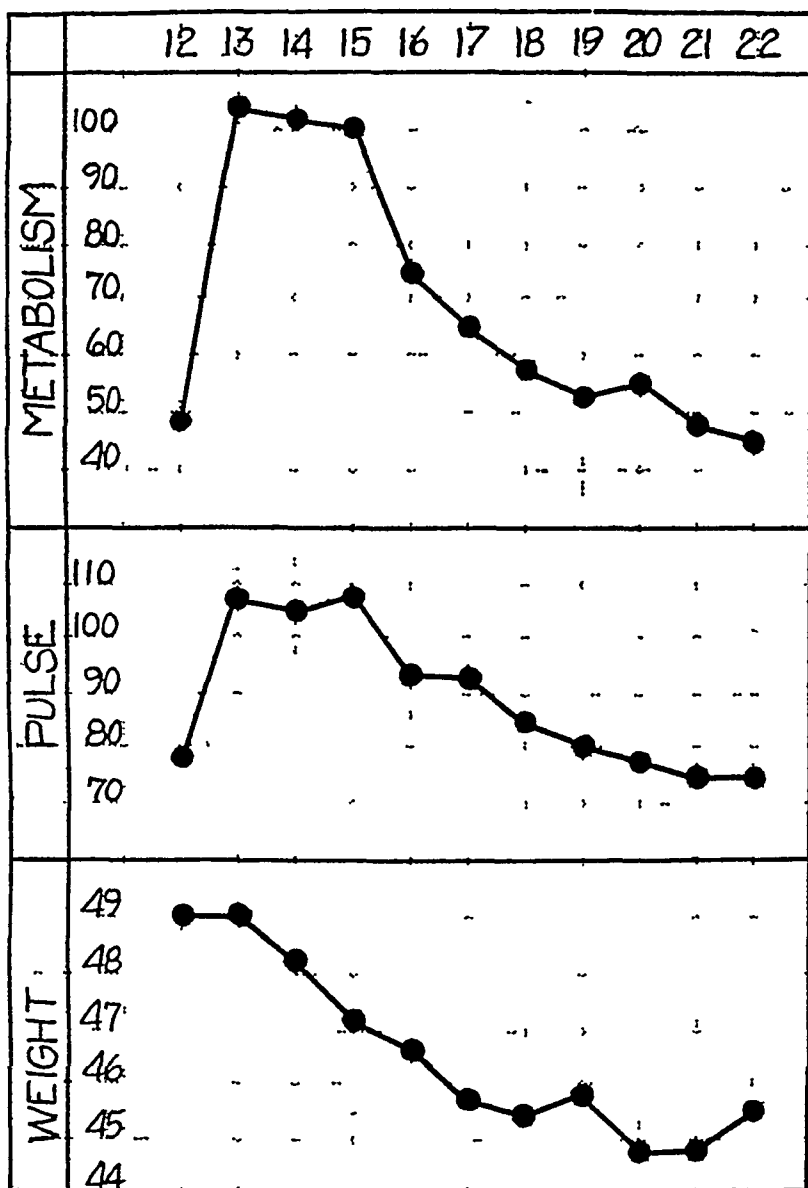


Chart 3—The effect of an acute tonsillitis with fever on the daily basal metabolism, resting pulse rate and body weight. The patient developed fever on the thirteenth of the month, which persisted until the seventeenth. The increase in the metabolism was approximately proportional to the degree of fever. The changes in the resting pulse corresponded to the variations in the basal metabolism. The decrease in body weight resulted from an increase in the metabolism and a diminished food intake.

An excellent opportunity was afforded to observe the subsequent results of an acute tonsillitis in the patient who was studied in this instance, as she was under observation for a period of 185 consecutive

days after the acute infection and has been seen at weekly intervals since then. Following the acute tonsillitis the patient's metabolism returned approximately to its previous level (49) as soon as the temperature became normal. Subsequent to this, for a period of 130 days, it remained in the vicinity of 40 per cent above the average

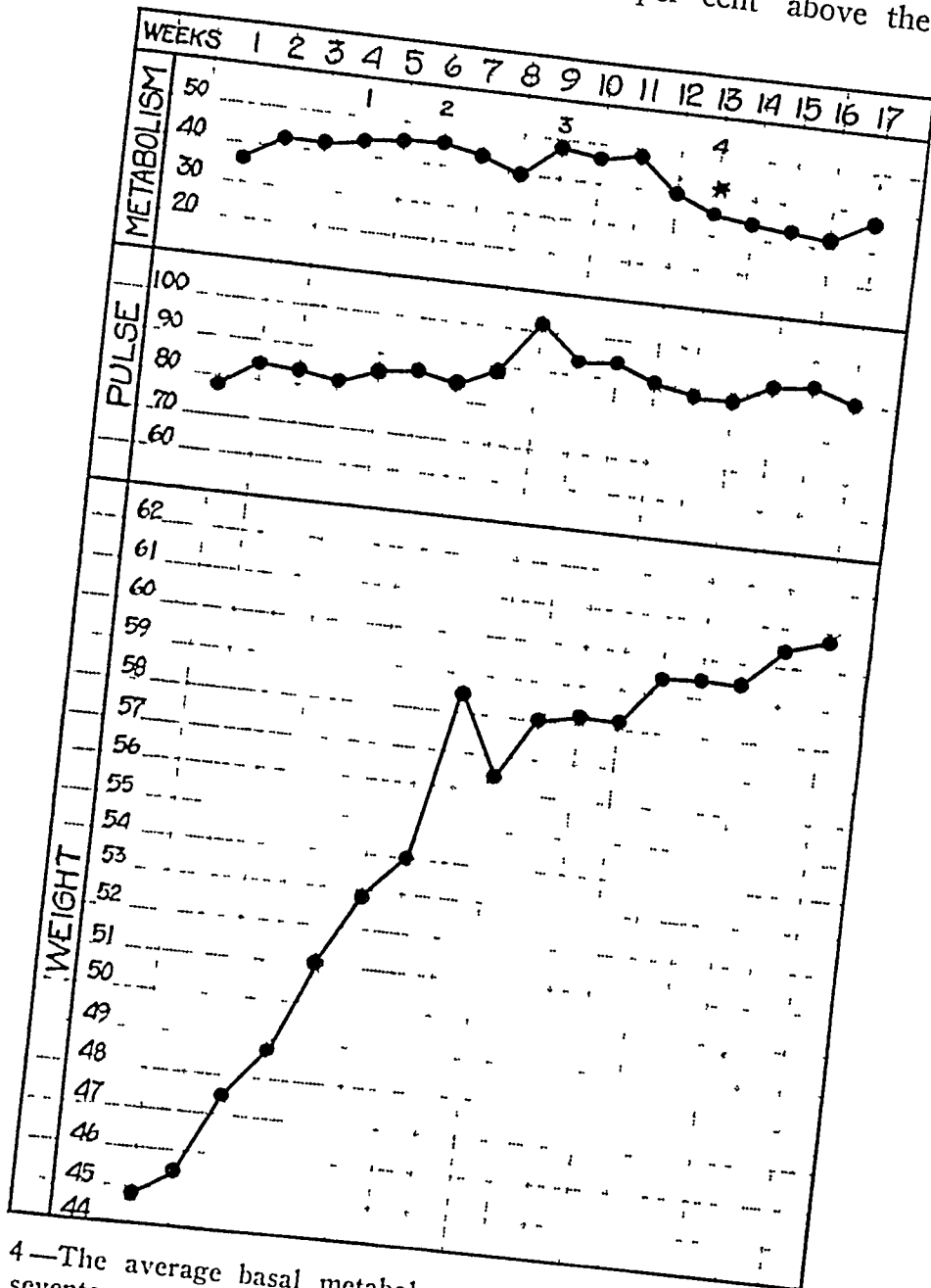


Chart 4—The average basal metabolism, pulse rate and body weight per week for seventeen weeks, from March 25 to July 29. The figures just above the metabolism curve indicate the times at which the four roentgen-ray treatments were given. The star represents the interval of six days when the patient was permitted to go home for six days. The only significant change shown in the chart is a gain of 16 kg in body weight. This is not interpreted as evidence of the beneficial effect of the roentgen-ray treatment, but was coincident with the development of an increase in appetite which permitted the patient to consume a large amount of food.

normal, while the pulse maintained a constant level of approximately 80 per minute. After the patient had been afebrile for four days, there was a great improvement in her appetite and from between 5,000 and 6,000 calories of food were consumed daily. As a result of this increased food consumption there was a gain in body weight of 16.3 kg in 121 days. The upward course of the weight curve began thirteen days after the period of fever and continued steadily until the peak was reached, 121 days later. For twenty-seven days following the febrile period the patient did not receive any treatment other than rest in bed and a high caloric diet. At the end of that time, however, the initial roentgen-ray treatment was given, and this was followed at intervals of approximately three weeks by three more, making in all four treatments. In summary, therefore, it might be said, that following the

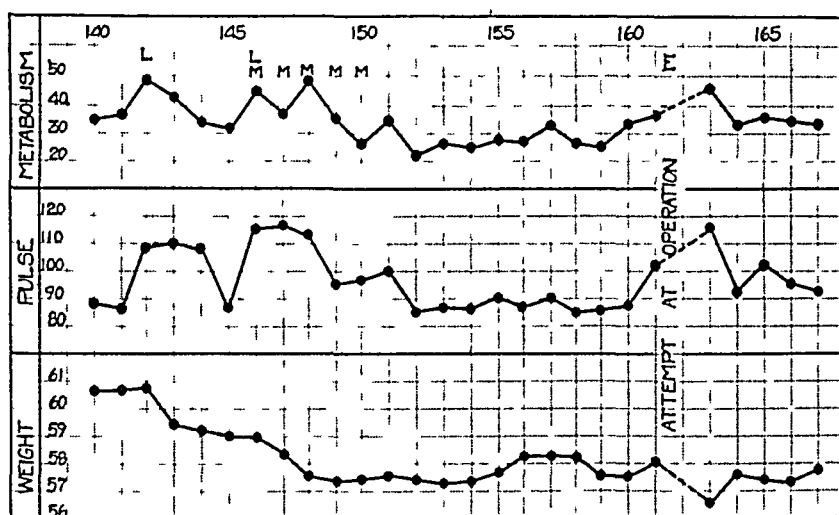


Chart 5—The effect of ligation of two thyroid arteries on the basal metabolism, pulse rate and body weight. The metabolism is expressed in percentage of normal, the pulse in beats per minute and the body weight without clothing in kilograms. *L*, indicates ligation of a thyroid artery, *M*, days during which the patient was menstruating, the figure at the top of the chart indicates the number of days the patient had been in the hospital, *E*, the day on which the patient was completely anesthetized but not operated on on account of the unfavorable reaction following the administration of the ether.

attack of acute tonsillitis the only change in the patient's condition was a gain of 16.3 kg in body weight in 121 days, while the pulse rate and metabolism remained unchanged. It seems unlikely that the enormous appetite, which caused the patient to consume such an excess of food, can be attributed to the influence of the acute infection on the thyroid gland. Furthermore, it seems logical to assume that a gain in body weight such as this, if it was due either to exhaustion of the thyroid gland or to actual destruction of a portion of its secretory tissue, would be accompanied by a reduction in the basal metabolism and pulse

rate, which in this case did not occur. Concerning this patient, therefore, it must be concluded that there is no clear evidence which indicates that the attack of acute tonsillitis exerted any influence on the subsequent course of the disease.

#### THE EFFECT OF ROENTGEN-RAY THERAPY

The influence of roentgen-ray treatment has been tried on a relatively small group of patients with exophthalmic goiter at this hospital, and the conclusions regarding the efficacy of this mode of treatment are not as yet permanent. A certain proportion of patients have made a satisfactory recovery following the use of this therapeutic agent. Even the most enthusiastic advocates of its use agree, however, that in some instances the patient fails to respond to this therapy even after prolonged and intensive use. Why some will and others will not improve following its use, has not been decided. The patient under observation apparently belonged to the group that does not respond, as four

TABLE 5—*The Effect of Four Roentgen-Ray Treatments on the Basal Metabolism*

	Dates	Days	Average Metabolism	Amount Gained in Body Weight, Kg
I Observation period	March 23 to April 11	23	+46	1.6
II Roentgen-ray treatments	April 15 to June 12	59	+45	9.6
III Observation period following treatments	June 13 to July 27	44	+40	2.7

roentgen-ray treatments at intervals of about three weeks had no apparent effect on the course of the disease. The first treatment was given after the patient had been resting in bed in the hospital for forty-five days. For the twenty-three days previous to the initial roentgen-ray treatment the average basal metabolism had been +46 per cent, while the maximum and minimum determination were +39 per cent and +52 per cent. When the daily metabolism results were charted, it was evident that the metabolic rate for these twenty-three days had struck a level, as there was no upward or downward tendency of the curve. The roentgen-ray treatments were given over an interval of fifty-nine days, during which time the average metabolism was +45, and the resting pulse rate showed no change of level. An additional period of forty-four days was allowed, following the fourth roentgen-ray exposure, to observe the effect of the treatment. The patient was inclined to think that she was "stronger" and was optimistic about her condition. The results of the metabolism determination and gain in body weight are shown in Table 5.



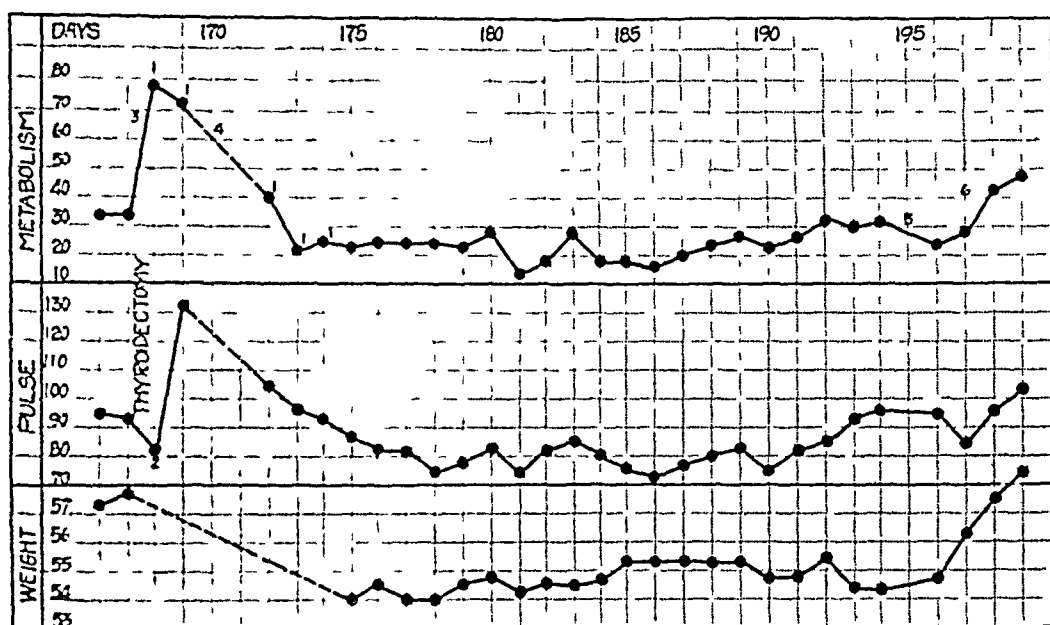
The interval including periods 2 and 3, a total of 103 days, was thought sufficient to observe the effect of roentgen-ray therapy. As shown by the table, there was no marked change in the average metabolic rate for the periods as 5 per cent is considered a permissible error, and the difference between the daily average in period 1 and period 2 is 5.8, a decrease which cannot be regarded as significant. The only evidence of improvement in the patient's condition is the substantial gain of 12.3 kg in body weight. This, however, cannot be used as convincing evidence of the action of the roentgen rays on the thyroid gland, as one would expect a gain in body weight due to this influence to be associated with a decreased metabolism.

#### THE EFFECT OF SURGICAL PROCEDURES

After the patient had been in the hospital for 148 days and her condition had remained stationary over a long interval despite rest, forced feeding and four roentgen-ray treatments, surgery was used as a therapeutic measure. On July 27, the one hundred and forty-eighth day of observation, the left superior thyroid artery was ligated under local anesthesia by Dr. John Homans of the surgical staff of this hospital, and four days later the same procedure was carried out on the right side. Four days after the second ligation the metabolism fell to +27 per cent, which was the first time in 157 days of observation that it had been so low. The average metabolism for the ten days immediately following the ligation was +27, and the minimum was 6 per cent below this. Following this transient drop, however, it again resumed its former preoperative level between +30 and +40 per cent above normal. Hence the improvement which followed the two ligations, as indicated by the decreased basal metabolism, was transient and slight. Sixteen days after the second ligation an attempt was made to perform a lobectomy, but the administration of the anesthetic was accompanied by such an alarming increase in the patient's pulse rate that the attempt was abandoned for that day. It is interesting to note that the patient's metabolism on the day following the complete anesthetization was +45 per cent, a rise of only 9 per cent above the basal metabolism on the day previous to administration of the anesthetic.

Six days after the attempted lobectomy the patient was operated on under local anesthesia by Dr. John Homans. During the operation the patient's condition again became precarious, and it was only possible to remove approximately one half of the thyroid gland as further surgical procedure at this time was not considered justifiable. About two hours after the operation the patient's condition had improved considerably, and it was possible to collect the expired air for a single period of six minutes. The basal metabolism for this period was found to be +79 per cent. A seven-minute period the following day showed

the metabolism to be  $+75$  per cent. For the following two days, the patient's condition was so serious that it was not considered wise to attempt metabolism determinations. On the fourth day after operation, the metabolism estimations were resumed, and from this time until the patient left the hospital, the average was as follows: first week,  $+26$  per cent, remaining nine days of the patient's stay in the hospital,  $+32$  per cent. The first obvious drop following the lobectomy occurred on the fifth day after operation when the metabolism was found to be  $+21$  per cent, while the lowest level of metabolism, which was  $+13$  per cent, occurred on the thirteenth day following operation. The metabolism remained at a comparatively low level for seven days, then gradually rose to a level between  $+25$  and  $+30$  per cent and



After leaving the hospital the patient remained at home resting in bed about half of each day. Weekly observations were made on her metabolism between September 19 and November 10. During this interval, her pulse rate and metabolism reached a level varying between 90 and 102 per minute for the former and between + 38 per cent and + 47 per cent for the latter. There was a gain in weight of 3.7 kg during this period. As the patient's condition was not improving, it was decided that a second operation was necessary to remove more of the thyroid gland. On November 13, Dr. David Cheever of the surgical staff performed this operation using local anesthesia. The patient made an uneventful recovery and on the sixth post-operative day her metabolism was found to be + 14 per cent and her pulse rate 66 per minute. It seems assured that her condition will continue to remain satisfactory.

#### EFFECT OF MENSTRUATION ON THE BASAL METABOLISM

Little is known concerning the effect of menstruation on the basal metabolism in normal women, or in women with exophthalmic goiter. Snell, Ford and Roundtree<sup>14</sup> refer to this subject and state that it may be of some practical clinical importance. These investigators studied the basal metabolism during the menstrual periods of ten normal women and drew the following conclusions concerning them. Two showed practically constant rises, while six showed constant rises, varying from 4 per cent to 14 per cent, the average being 10 per cent, while in two a drop in rate was encountered. The rise, when it occurs, is in the menstrual or premenstrual period and is followed by a post-menstrual fall. Values outside of normal limits (10 per cent above or below the average normal) were infrequent.

The patient who was observed during this study passed through seven menstrual cycles. Each period varied from five to six days, and was not accompanied by pain or other subjective sensations. Chart 7 indicates the metabolic rate during six periods. The metabolism during the seventh menstrual period was influenced by lobectomy, so no definite conclusion could be deduced. The first menstrual period occurred in the initial two weeks of the patient's stay in the hospital, and it was during this interval that the greatest fluctuations were present in the metabolism. It is, therefore, exceedingly difficult to estimate the influences of any factor on the metabolism at this time. The second and third menstrual periods showed a curious agreement in their fluctuations. If the rise which occurred on the first day of these periods is due to the appearance of the menstrual function, it is a small increase, as it amounts to only 5 per cent, which is just the limit of error. The fall

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14 Snell, A. M., Ford, Francis, and Roundtree, L. G. *Studies in Basal Metabolism*, J. A. M. A. **75** 515 (Aug. 21) 1920.

on the second day of the menstrual period in these curves is of greater extent as it amounts to approximately 10 per cent. Curves 4 and 5 of the fourth and fifth menstrual periods do not confirm the changes observed in curves 2 and 3. Curve 6 cannot be used as on the initial day of the menstrual function the right superior thyroid artery was

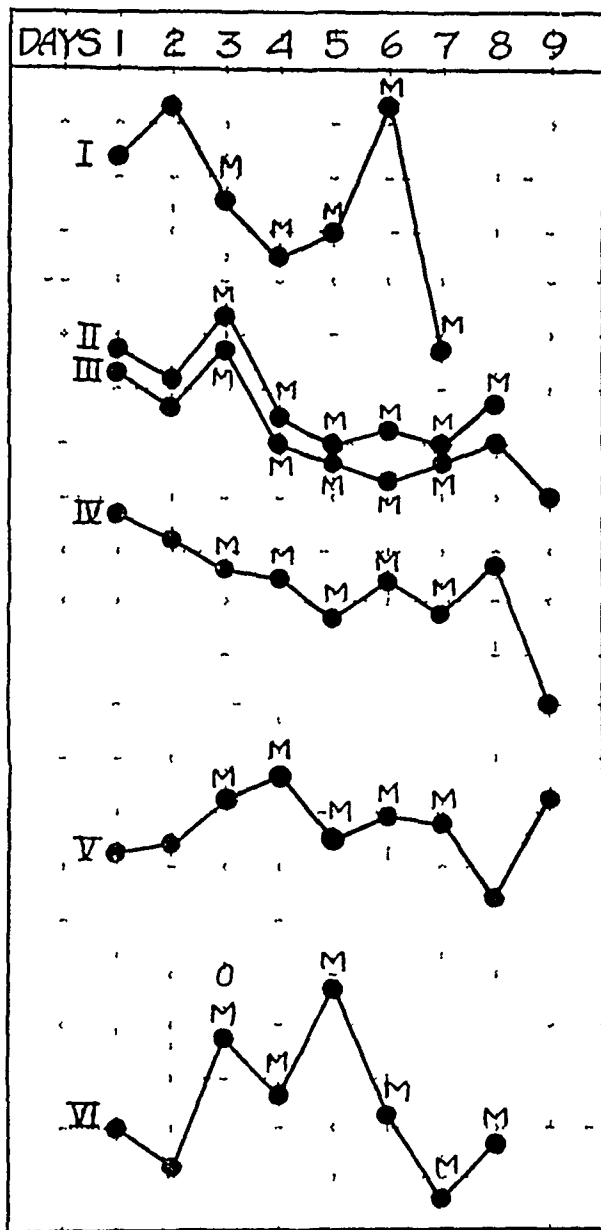


Chart 7—The effect of the menstrual cycle on the daily basal metabolism. The metabolism is charted for each day for an interval varying from seven to nine days during the six menstrual periods which the patient passed through while under observation. Each space in a perpendicular direction represents a change of 5 per cent in the metabolism. *M*, represents days when patient was menstruating, *O*, ligation of the right superior thyroid artery. The first cycle occurred shortly after the patient was admitted, when her condition was very unstable. The sixth was influenced by ligation of the right superior thyroid artery. From the foregoing observations it was concluded that menstruation had no effect on the basal metabolism.

ligated, which in itself is sufficient to account for the rise in metabolism on that particular day and for the subsequent fluctuations. From the observations on this patient, therefore, it must be concluded that the metabolic rate was slightly, if at all, influenced by the menstrual function.

#### CONCLUSIONS

A patient with exophthalmic goiter was observed while at rest in bed in the hospital from March 1, 1922, to September 19, 1922, an interval of approximately six and a half months. During this time the basal metabolism, resting pulse, food intake and body weight were determined practically every day. The following conclusions have been drawn from this study.

1 The basal metabolism may be determined within a limit of 5 per cent error, and in a great majority of instances this error may not exceed 3 per cent.

2 The initial metabolism of a patient with exophthalmic goiter may be much higher than the subsequent metabolism, and even after a rest in bed of ten days the fluctuation in the metabolism from one day to the next may be as great as 23 per cent.

3 After a rest of several weeks in bed there was a tendency for the basal metabolism in this particular patient to become stabilized, and for a period of several months the variation on consecutive days rarely exceeded 5 per cent.

4 The body weight of a patient with exophthalmic goiter may remain stationary, increase or decrease, irrespective of the level of the basal metabolism, dependent on the amount of food consumed. Most frequently the appetite of such a patient is good or abnormally increased, despite this, the body weight decreases.

5 The number of calories adequate to maintain a patient with exophthalmic goiter in caloric balance, when resting in bed, may be estimated as approximately an 85 per cent increase over the number of calories which represent the patient's basal metabolism for twenty-four hours.

6 Acute infections, such as an acute tonsillitis with fever, may exert a serious influence on a patient with exophthalmic goiter, owing to the great excess of heat produced and the large amount of weight which is lost as a consequence of a high basal metabolism and a small food intake. In this particular patient no beneficial effect as a result of the acute tonsillitis was observed in the subsequent course of the thyroid gland disorder.

7 The menstrual periods did not exert an appreciable effect on the basal metabolism in this patient.

8 Four roentgen-ray treatments over the thyroid gland at intervals of three weeks had no effect on the course of the disease

9 Ligation of two thyroid arteries was followed by a transient drop in the daily basal metabolism, and removal of approximately half of the gland had a similar effect

# THE EFFECT OF ALKALIS ON GASTRIC SECRETION AND MOTILITY AS MEASURED BY FRACTIONAL GASTRIC ANALYSIS

BRUCE C LOCKWOOD, M D, AND HAZEN G CHAMBERLIN, M D  
DETROIT

The object of this work was to determine by fractional analysis, in a sufficiently large number of persons, two points (1) whether or not alkalis in addition to their immediate neutralizing effect also produce a secondary rise of acidity greater than that which occurs in a person without their administration, (2) what effect alkalis have on gastric motility

Without extensively quoting the early literature on the subject, it is sufficient to state that there has always been a difference of opinion as to whether alkalis act as a stimulant or depressant to gastric secretion. The defenders of the alkaline Spa treatments held that while at times an alkali might act as a stimulant shortly after taking, the prolonged administration caused a gastric catarrh with associated decreased secretion. Those who believed that alkalis acted only as a depressor of gastric secretion were supported by Pawlow's observation<sup>1</sup> that on a dog, soda produced a diminution of all the alimentary secretions.

On the other hand, many early French and German investigators, especially the clinicians, held that alkalis in any dosage acted only as a stimulant.

The more recent textbooks and articles dealing with this subject reflect the different views, although we could find no one investigation in which accurate methods were used on a sufficiently large number of subjects to draw definite conclusions.

Cushny<sup>2</sup> states that it has been demonstrated experimentally on dogs that alkaline carbonates do not influence the gastric secretion any more than free water. Gross and Held<sup>3</sup> say that alkalis before or with meals increase acidity. Hemmeter<sup>4</sup> does not believe that alkalis increase secretion, but that if they are taken before meals, they may act as a temporary irritant, just as saline in the nose would excite a mucous flow. Bassler<sup>5</sup> thinks that alkalis do not stimulate secretion and may be kept up for long periods of time without harm.

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1 Pawlow The Work of the Digestive Glands, Philadelphia, J B Lippincott Co., 1910

2 Cushny, A R Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1915

3 Gross, M H, and Held, I W Therapeutics of the Gastro-Intestinal Tract, New York, Rebman Co., 1913

4 Hemmeter Diseases of the Stomach, Philadelphia, P Blakiston's Son & Co., 1917

5 Bassler, A Diseases of the Stomach and Upper Alimentary Tract, Philadelphia, F A Davis Co., 1917

Crohn,<sup>6</sup> with the fractional method, investigated the action of different doses of bismuth subnitrate, magnesium oxid, and sodium bicarbonate, given at different times in relation to the test meal. His conclusions, however, are based on only one or two observations with any one method of administration and should be accepted with reserve in view of the variations which one sees in the response of the stomach at different times. He states that the administration of either soda or magnesia is followed by an irritative reaction in which the acid mounts quickly to at least the level of the control test at the corresponding time, and in most cases exceeds it.

Fowler, Spencer, Rehfuess and Hawk<sup>7</sup> state that the stomach tends to bring its contents to a normal acid level, regardless of the reaction of ingested substances, that is, it lowers acidity when strong acids are introduced, and raises acidity when alkalis are given.

Regarding the effect of alkalis on motility, the literature is scanty. Ladd,<sup>8</sup> experimenting on a series of children, found that bismuth and other alkalis hastened the emptying time of the stomach. Spencer, Meyer, Rehfuess and Hawk<sup>9</sup> found that 5 per cent soda solution was held in the stomach until reduced, and that a 1 per cent solution hastens the emptying time. Carlson reports<sup>10</sup> that 1 per cent sodium carbonate solution inhibits gastric contractions for a short time, as water does, and is due to the bulk of the solution.

#### METHOD OF PROCEDURE

The method employed in the following experiments is identical with that used in previous work, reports of which have been published.<sup>11</sup> The subject on a morning fasting stomach swallowed the small fractional tube, and the fasting contents were aspirated. An Ewald meal was then given with the tube left in place and from 5 to 10 c.c. were aspirated every fifteen or twenty minutes.

When the return was free from bread, this point was taken as the evacuation time. The free and total acidity was determined by the Toepfer method. All patients had been previously tube broken. The

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6 Crohn, B. B. Effect of Antacid Medication on Gastric Secretion and Acidity, *Am J M Sc* **155** 801, 1918.

7 Fowler, C. C., Spencer, W. H., Rehfuess, M. E., and Hawk, P. B. Gastric Analysis. IV. The Gastric Equilibrium Zone, *J A M A* **77** 2118 (Dec 31) 1921.

8 Ladd, Influence of Alkalies on Gastric Motility, Boston M & S J **170** 518, 1914.

9 Spencer, W. H., Meyer, G. P., Rehfuess, M. E., and Hawk, P. B. *Am J Physiol* **39** 459, 1916.

10 Carlson, A. J. Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916.

11 Lockwood, B. C., and Chamberlin, H. G. The Effect of Olive Oil on Gastric Function as Measured by Fractional Analysis, *Arch Int Med* **31** 96 (Jan) 1923.



normal curve, and the curve after the administration of alkali were all taken within a few days of each other and an effort made to keep the subject on the same general routine, diet and water intake. In securing the test curves, the alkali was given in the water of the test meal.

### RESULTS

*Sodium Bicarbonates*—The effect of administration of 4 gm doses of this drug, given with the test meal, was observed on eight carefully controlled cases. The average free hydrochloric acid was higher than the control in only one case, while the general average for the series was reduced from 40.6 degrees in the controls to 31.7 degrees after the soda. The average total acidity was higher than the control in two cases, while the average for the series was reduced from 54.8 degrees to 44.1 degrees after the soda. The free hydrochloric acid rose to a

TABLE 1—Results of Administration of 4 gm of Sodium Bicarbonate with the Ewald Meal in Eight Cases

Case	Average Free Acid		Average Total Acid		Maximal Free Acid		Maximal Total Acid		Evacuation Time		Bile	
	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control	Test	Control	Test
G S	36	60.2	54.1	72.9	60	98	80	104	80	120	0	+
F M	22	18.7	29.4	27	40	42	50	60	100	100	0	0
A D	40	16.1	52	22.3	51	25	66	32	120	120	0	0
J M	37	35.5	54.2	51.2	56	60	72	80	100	120	0	0
P G	37.2	37.1	42	47.2	63	60	70	76	120	80	0	0
H G	51.2	37.8	67.7	32.8	60	73	78	88	105	75	+	0
A G	43.7	17.7	65	22.7	72	40	93	46	135	75	0	0
A S	58.2	30.6	74	47.2	78	55	97	73	135	135	0	0
Average	40.6	31.7	54.8	44.1					112	103		

higher point on the curve after the administration of soda than in the control in four, or one-half, of the total eight cases. The total acidity attained a higher point in five cases.

The average evacuation time in the controls was 112 minutes, while after soda, it was 103 minutes, only a slight reduction. Bile regurgitation was observed in one control curve and in one curve after the administration of soda. Table 1 shows these results in convenient form.

In Chart 1 are plotted five total acidity curves on the same patient (H G—duodenal ulcer). All these observations were made within two weeks. The two control curves (dotted) run practically the same. Two curves are shown in which 4 gm of sodium bicarbonate were given with the test meal. One remained low while the other rose within forty-five minutes to about the same maximal height as the control curves. One curve (No. 3) shows a case in which 4 gm of soda were given thirty minutes after the meal. The acid promptly dropped, but within another thirty minutes had risen to about the same level as in the controls, to fall slowly again as digestion proceeded.

*Calcium Carbonate*—In this series of six cases, 4 gm of the drug were given with the meal and comparison made with the control curves

The average free hydrochloric acid was lower after the alkali in all observations, and for the series was reduced from an average of 32.1 degrees in the control curves to 11.9 degrees after the calcium carbonate. The average total acidity was higher after the drug in two cases, but the average for the series was reduced from 54.8 degrees in the controls to 44.1 degrees after the calcium carbonate. The free hydrochloric acid attained a higher point in two cases, and the total acidity in three cases, after the medication than in the six corresponding control curves.

The average evacuation time was almost the same, 100 minutes for the controls and 103 minutes for the calcium carbonate. Bile was seen

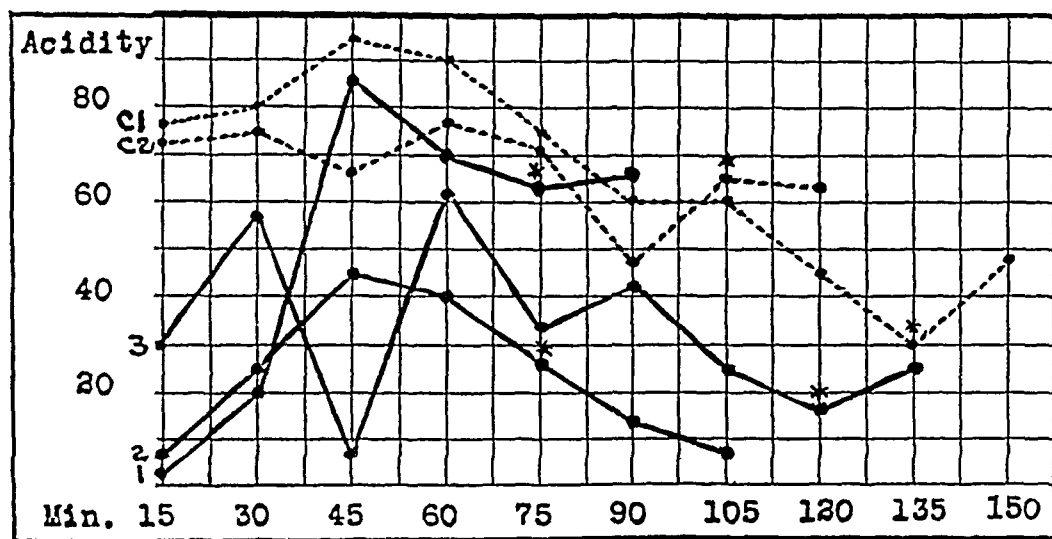


Chart 1—Acidity curves in subject H. G. C1 indicates the control curve on January 21, C2, the control curve on January 30, 1, the curve after 4 gm of sodium bicarbonate were given with the Ewald test meal on January 24, 2, the curve on January 30 after the same test, 3, one-half hour after ingestion of the Ewald test meal. The star in this and the following charts indicates that bread was absent.

in one curve after medication and in none of the controls. Table 2 shows these results.

*Magnesium Oxid*—With this alkali the effects were observed in five cases. Two grams were given with the meal.

The average free hydrochloric acid was lower in all cases, and the average for the series was reduced from 35.3 degrees in the controls to 15.5 degrees after the administration of the magnesia.

The average total acidity was also lower in every observation and for the series was reduced from 50.5 to 20.2 degrees.

The free hydrochloric acid and also the total acidity rose to a higher point after this alkali in only one of the five cases. The average

evacuation time was exactly the same, 104 minutes in both the control and test observations. Bile was observed once in the test curves and not at all in the control curves. In Table 3 these results are tabulated.

TABLE 2—Results of Administration of 4 gm of Calcium Carbonate With the Ewald Meal in Six Cases

Case	Average Free Acid		Average Total Acid		Maximal Free Acid		Maximal Total Acid		Evacuation Time		Bile	
	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control	Test	Control	Test
G S	36	13	54.1	9.3	60	8	80	18	80	100	0	+
A D	40	20.8	52	27.2	51	76	66	82	120	120	0	0
P G	37.2	34.3	12	41.0	63	78	70	86	120	100	0	0
M M K	42.6	9.4	62.3	18.4	67	32	77	43	80	100	0	0
S W	Achillia		2.5	4.9	0	0	5	10	100	100	0	0
B M	37	6.1	54.2	18.6	56	25	72	42	100	100	0	0
Average	32.1	11.9	44.5	19.8					100	103		

TABLE 3—Results of Administration of 2 gm of Magnesium Oxide with the Ewald Meal in Five Cases

Case	Average Free Acid		Average Total Acid		Maximal Free Acid		Maximal Total Acid		Evacuation Time		Bile	
	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control	Test	Control	Test
A L	26.4	21.6	50.4	33.4	35	58	54	88	100	120	0	0
P G	37.2	6.0	42	17.7	63	24	70	54	120	80	0	+
J M	37	10.8	54.2	22.0	56	36	72	48	100	100	0	0
A D	40	15.6	52	20.5	51	60	66	66	120	120	0	0
G S	26	23.4	54.1	27.4	60	50	80	57	80	100	0	0
Average	35.3	15.5	50.5	20.2					104	104	0	0

TABLE 4—Results of Administration of 4 gm of Bismuth Subnitrate with the Ewald Meal in Seven Cases

Case	Average Free Acid		Average Total Acid		Maximal Free Acid		Maximal Total Acid		Evacuation Time		Bile	
	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control Curve	After Alkali	Control	Test	Control	Test
G S	36	63.8	54.1	70.5	60	84	80	88	80	80	0	0
J M	37	29.9	42	39.4	63	40	70	70	120	80	0	0
A D	40	23.1	52	36.7	51	30	66	43	120	100	0	0
A L	26.4	16	50.4	26.6	35	30	54	44	100	120	0	0
M K	42.6	39	62.3	50.6	67	56	77	70	80	100	0	0
H G	51.2	73.5	67.7	90.9	60	90	78	97	105	135	+	0
P G	37.2	26	42.2	38.1	63	34	70	45	120	100	0	0
Average	38.6	38.7	52.9	50.4					103	102		

*Bismuth Subnitrate*—The effect of this drug was studied in seven cases. A dose of 4 gm was given with the meal in each test.

The average free hydrochloric acid, total acidity and evacuation time were practically the same before as after its administration. The free

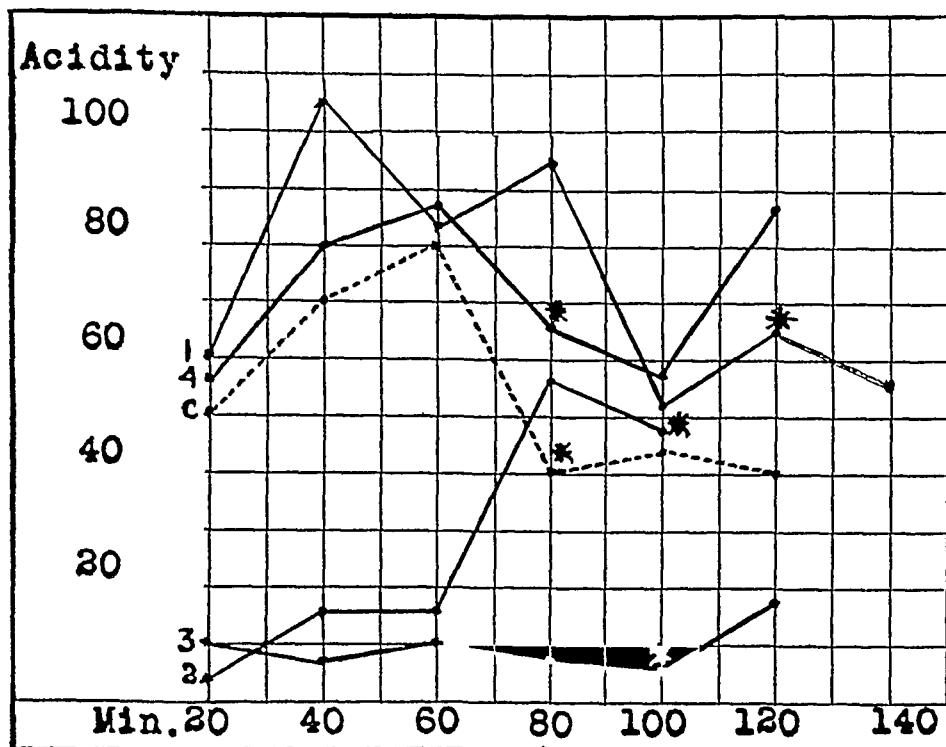


Chart 2—Effect of four alkalis on subject G S In this and the following charts, C indicates the control curve after the ingestion of the Ewald test meal, 1, the curve after the ingestion of 4 gm. of soda with the test meal, 2, after the ingestion of 2 gm of magnesium oxid with the test meal, 3, after the ingestion of 4 gm of calcium carbonate with the test meal, 4, after the ingestion of 4 gm of bismuth subnitrate with the meal

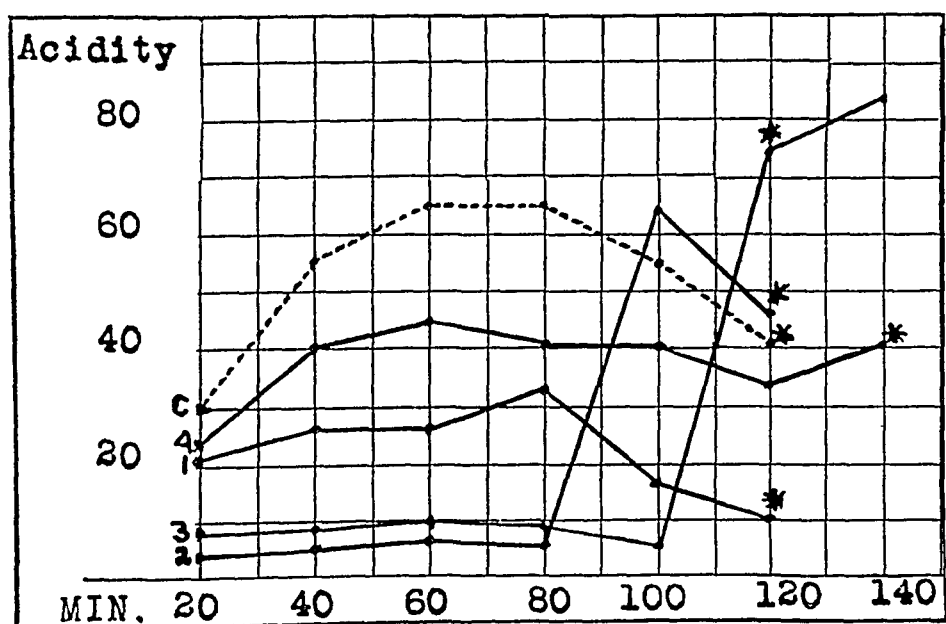


Chart 3—Effect of four alkalis on subject A D

and total acidity both rose to a higher point in only two of the test curves. Bile was seen in one of the control curves and in none of the test curves. These results are shown in Table 4.

The effect of four alkalis on the curve of the same person are shown for four different subjects. Charts 2, 3, 4 and 5 each show a control

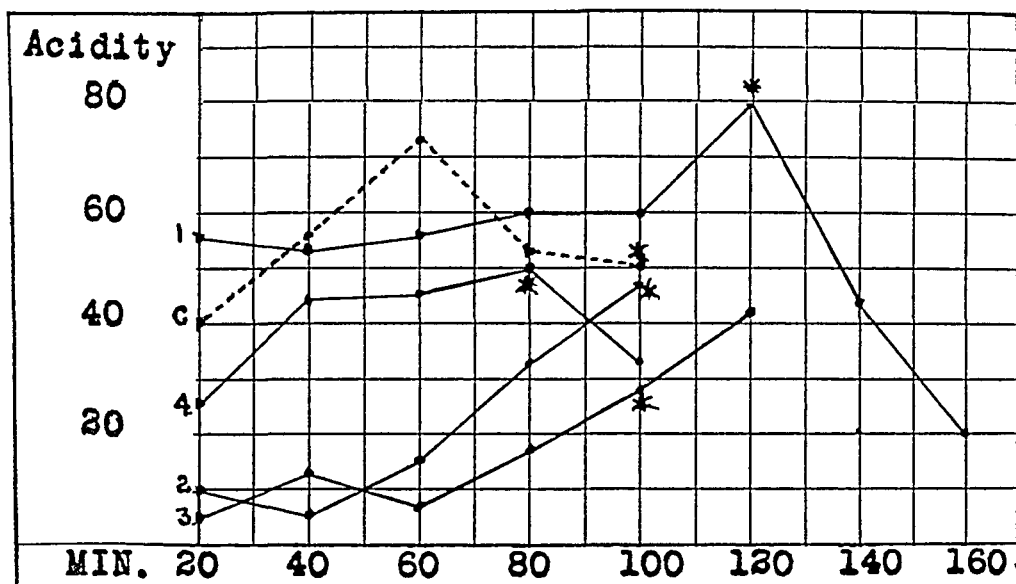


Chart 4—Effect of four alkalis on subject J M

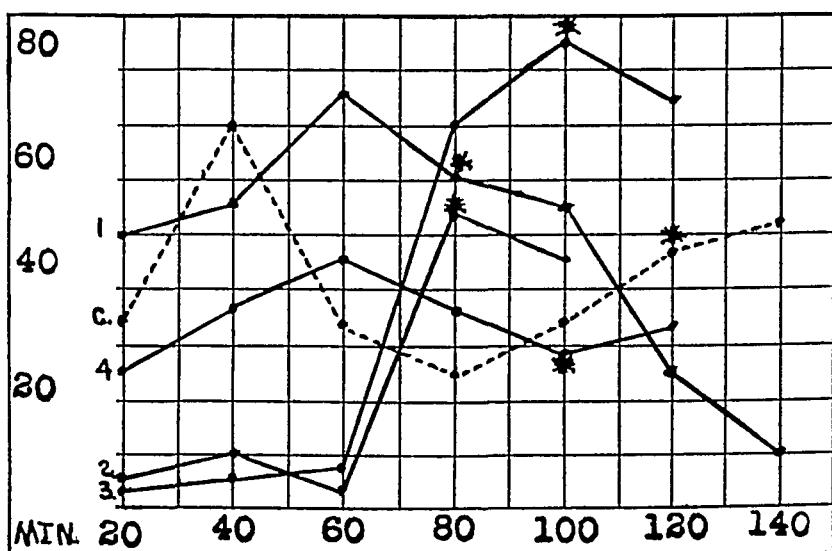


Chart 5—Effect of four alkalis on subject P G

curve of total acidity (dotted) on four different persons assumed to be free from gastro-intestinal disease. With each control are also shown curves obtained after the administration of the four different alkalis studied. These curves are self explanatory. They were all taken within one week.

## SUMMARY AND COMMENT

The effect on gastric function of the administration of a standard dose of four different alkalis is studied. They were all given with the Ewald meal and comparison made with control curves in twenty-six cases.

Neither sodium bicarbonate, calcium carbonate, magnesium oxid or bismuth subnitrate seemed to affect the evacuation time of the stomach. This does not support Cannon's<sup>12</sup> conception of the acid control of the pylorus. The phenomenon of bile regurgitation was also unaffected.

The average free and total acidity was lower after the administration of the alkali in all observations on calcium carbonate and magnesium oxid. In less than one fourth of the sodium bicarbonate tests it was higher. The average acidity was unaffected by bismuth subnitrate.

After sodium bicarbonate the acidity rose to a higher point than in the controls in about one half of the cases, after calcium carbonate, in one fourth, and after magnesium oxid, in one fifth of the cases. After bismuth, the acidity attained a higher point in only two of seven cases.

As the neutralizing power of soda is about one half that of calcium carbonate and one fourth that of magnesium oxid, it is apparent that the dose of soda which we used (4 gm) was only one half as strong a neutralizer as was our dose of calcium carbonate (4 gm) and magnesium oxid (2 gm). It is possible that with a dose of soda equal in strength to the dose of calcium or magnesium the acid rebound would have been less in evidence. On the other hand, the liberation of carbon dioxide when soda is given may act as a direct stimulant. This point remains to be cleared up.

## CONCLUSIONS

Sodium bicarbonate in 4 gm doses, in addition to its immediate neutralizing effect, causes a rebound of acidity to a point higher than would normally have occurred in about one half the cases. Calcium carbonate (4 gm) and bismuth subnitrate (4 gm) produce this effect in only one fourth, and magnesium oxid in only one fifth, of the cases, while the average acidity during the digestive phase following their administration is much lower in seven eighths of the cases.

The common alkalis in the foregoing dosage do not effect the evacuation time of the stomach for the Ewald meal.

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<sup>12</sup> Cannon, W. B. *The Mechanical Factors of Digestion*, New York, Longmans, Greene & Co., 1911.

# ACUTE LYMPHADENOSIS COMPARED WITH ACUTE LYMPHATIC LEUKEMIA

HAL DOWNEY PH D, AND C A MCKINLAY, MD  
MINNEAPOLIS

## PART I CLINICAL STUDY \*

C A MCKINLAY, MD

Numerous reports are found in medical literature describing groups of cases which, on account of clinical features and blood cell changes, have been thought to be similar to and often confused with acute leukemia. Naegeli<sup>1</sup> mentions cases of sepsis with low total leukocyte counts and relative increase in the lymphocytes, and also acute febrile affections with high absolute lymphocyte counts with atypical forms. It is pointed out that this lymphatic reaction is more confusing where there is also an absolute lymphocytosis with atypical lymphocytes. Further, with a clinical picture of fever, prostration and enlargement of lymph nodes and spleen, it may be impossible to differentiate these cases from leukemia until recovery occurs. Naegeli quotes Turk and others who report cases of angina and streptococcus sepsis with lymphatic reaction and recovery, besides cases of acute infection, such as pneumonia, scarlet fever, erysipelas, meningitis, typhus and malaria, in which the blood picture showed frequent myelocytes, erythroblasts and severe anemia. Turk considered that there was some relationship between infection with lymphatic reaction and leukemia. Herz<sup>2</sup> mentions that in certain infections there are cases in which the blood picture simulates a lymphatic leukemia, and only recovery makes the diagnosis clear. Cabot<sup>3</sup> reports four cases of acute infection, including lymphangitis, furunculosis, streptococcus sore throat and cervical adenitis, all of which showed lymphocytosis and might be confused with leukemia. His observations are apparently based more on the clinical than on the blood picture resemblance. Sanders<sup>4</sup> reports a case with fatal Ludwig's angina, lymphocytosis and anemia.

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\* From Students' Health Service and Department of Medicine, University of Minnesota

1 Naegeli, O. Blutkrankheiten und Blutdiagnostik, Berlin and Leipzig Vereinigung wiss. Verleger, W. de Gruyter & Co., 1919

2 Herz, A. Die akute Leukämie, Leipzig, Franz Deuticke, 1911

3 Cabot, R. C. The Lymphocytosis of Infection, Am J Med Sc vol 145, p 335

4 Sanders, W. E. The Nature of the Lymphocytosis of Acute Infections, Jour Lab Clin Med 4 344, 1919

Some English observers<sup>5</sup> and others, including Morse,<sup>6</sup> apparently consider cases with lymphatic reaction to be similar to glandular fever. This disease was first described by Pfeiffer,<sup>7</sup> who pointed out its epidemic nature, its occurrence in children, its characteristics of nontender cervical glandular enlargement, the absence of tonsillitis, the slight injection of the throat, abdominal pain and enlargement of the liver and spleen. West<sup>8</sup> reported an epidemic of ninety-six cases limited to children, a majority of whom showed no evidence of throat infection. Tidy and Morley<sup>9</sup> have recently reported cases and described the disease again. They, with most other observers since Pfeiffer, have frequently noted, in addition, the enlargement of the axillary and inguinal glands but not the abdominal signs. Occasionally infection has taken place in adults, with the same important clinical features. Where a blood examination was made, lymphocytosis often was present, with moderate increase in the total number of white blood cells. Since few blood examinations have been reported, the chief features available to define this group are clinical. These features which all together present a distinct entity are: epidemicity, chief incidence in children, absence of tonsillitis, general glandular enlargement and frequent enlargement of the liver and spleen. Most observers consider the disease to be due to a specific unrecognized organism.

On the other hand, Sprunt and Evans,<sup>10</sup> Bloedorn and Houghton,<sup>11</sup> and Cross<sup>12</sup> and others have reported cases, the main clinical features of which have separated them from the groups just mentioned. The characteristics of these cases are: the occurrence in young adults of infection of the upper respiratory tract with systemic reaction always present, but never severe, besides the general glandular enlargement with frequent enlargement of the spleen. The cases have all shown a lymphocytosis and moderate increase in the total number of white blood cells, together with a blood picture which might be confused with acute leukemia. In none have hemorrhages or severe anemia been reported.

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5 Editorial. *Brit M J* **1** 649, 1921.

6 Morse, P. F. Glandular Fever, *J A M A* **77** 1403 (Oct. 29) 1921.

7 Pfeiffer, E. Drusenfieber. *Yahrb f Kinderh* **29** 257, 1889.

8 West. *Arch Pediat* **13** 889, 1896.

9 Tidy and Morley. Glandular Fever, *Brit M J* **1** 452 (March 26) 1921.

10 Sprunt, T. P., and Evans, F. A. Mononuclear Leucocytosis in Reaction to Acute Infections, *Johns Hop Hosp Bull* **31** 357, 1920.

11 Bloedorn, W. A., and Houghton, J. E. The Occurrence of Abnormal Leukocytes in the blood in Acute Infections, *Arch Int Med* **27** 315 (March) 1921.

12 Cross, J. G. Conditions Simulating an Acute Leukemia (Acute Benign Leukemia), *Minnesota Med*, October, 1922, p. 579.



Since completion of this study, Longcope<sup>13</sup> has reported a series of ten cases, several of which are similar to ours. Only five patients had acute throat infection, and his Cases 1 and 2 showed no leukocytosis and only a very moderate increase in lymphoid cells. The histology of an excised lymph node in Case 2 suggested Hodgkin's disease and was unlike that in our Case 7, or that reported by Evans and Sprunt. These variations may cast some doubt as to whether his Cases 1 and 2 have sufficient clinical features to be grounds for inclusion in the group described by the last mentioned observers.

To such cases are added, in this paper, nine which were observed recently within a relatively short period of time. Their frequency suggests a much more common occurrence of the disease than is recognized at present and arouses curiosity as to its etiology. A better understanding of this type of case is desirable, not only that diagnosis and prognosis may be more certain, but that evidence may be accumulated concerning its etiology and the possible relationship to leukemia. While most of these cases, on account of their benign nature and short course, may be classified as a clinical entity and recognized without difficulty, occasional members of the group present not only clinical features but blood pictures that do not readily allow such disposal. Whether or not the cause of this disease is a specific organism is a problem concerning which no proofs are available. The usual assumption has been that such lymphatic reaction occurs with various types of infection that are usually associated with polymorphonuclear leukocytosis. The variations that have occurred in the nature of acute infections, such as influenza and encephalitis, may have a bearing on the increased frequency of the type of case here reported. Case history 1 is given in some detail. Others have been abbreviated to include only important positive findings.

#### REPORT OF CASES

**CASE 1—History**—M. J., a white man, aged 22, single, a student, entered the Students' Health Service Hospital, March 1, 1921, complaining of sore throat, fatigue and headache. He had had scarlet fever at the age of 9 years, he had also had measles, mumps and whooping cough during childhood. While stationed with the army in Texas in 1916, the patient had had a period of diarrhea and chills. He said that he had noticed slight loss of strength one month previous to entrance. On February 28, the patient first appeared at the dispensary complaining of a sore throat. The following day he returned with a temperature of 101.6 F. and was admitted to the ward, on the nose and throat service.

**Physical Examination**—On the date of admission the throat was moderately injected and on both tonsils were scattered patches of grayish white exudate. Cultures showed no predominating organism. On March 6, medical consulta-

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<sup>13</sup> Longcope, W. T. Infectious Mononucleosis (Glandular Fever), with a Report of Ten Cases, *Am J Med Sc* **164** 781 (Dec.) 1922.

tion was requested. Examination showed a well developed and well nourished young man without marked prostration or anemia. The throat showed marked injection, which involved the tonsils, fauces and postpharyngeal wall. The tonsils showed a few small areas of exudate and ulceration. These later became enlarged and presented quite marked ulcerative areas. In the mucous membranes over the soft palate and anterior pillars, extending to the buccal mucosa, were several hemorrhagic areas. These persisted throughout the period of observation. The cervical lymph nodes were markedly enlarged and greater on the left, where they formed a mass from four to five cm in diameter.

TABLE 1—*Blood Findings in Case 1*

Date	Red Blood Cells	Hemoglobin, per Cent	White Blood Cells	Polymorphonuclears, per Cent	Polymorphonuclear Eosinophils, per Cent	Polymorphonuclear Basophils, per Cent	Lymphocytes, per Cent	Small Lymphocytes, per Cent	Large Lymphocytes, per Cent	Transitionals, per Cent	Large Mononuclears, per Cent	Unclassified
3/ 6/21	4,672,000	95	3,000	13	1		86					
3/ 7/21			4,500	18	1		80					
3/ 9/21				18	1	1	80					
3/11/21	3,904,000			6 66	0 33	1	81					
3/12/21			17,200	18								
11/ 3/21			7,000	50		1		8	37	4		
11/25/21			7,900	66	1			3	23	2	4	
2/10/22			7,200	45	1			36	15		3	
2/24/22			7,150	55				21	17	4	3	
6/ 8/22				70	1			29				1

TABLE 2—*Blood Findings in Case 2*

Date	Red Blood Cells	Hemoglobin, per Cent	White Blood Cells	Polymorphonuclears, per Cent	Polymorphonuclear Eosinophils, per Cent	Polymorphonuclear Basophils, per Cent	Small Lymphocytes, per Cent	Large Lymphocytes, per Cent	Transitionals, per Cent	Large Mononuclears, per Cent
11/2/21			14,450	19 5			9	60	10 5	1
11/3/21	6,400,000	85	16,100	21			8	67	4	
11/7/21	1,840,000		15,600							

The glands were discrete, of firm consistency and slightly tender. The axillary, epitrochlear and inguinal glands were also definitely enlarged and slightly tender. The thorax and heart were essentially negative. The spleen was definitely palpable. At this time the total leukocyte count (Table 1) was 3,000 with 86 per cent of lymphocytes. The total leukocyte count increased to 17,200 and the lymphocyte count stayed above 80 per cent. The red cells dropped from 4,600,000 to 3,900,000 while the patient was under observation in the hospital. The temperature was irregularly intermittent and reached a maximum of 103 F. The pulse was not rapid and averaged between 70 and 80.

Prostration was moderately severe. The physical condition and fever of the patient showed no marked change up to March 13, when he was discharged. At that time the diagnostic impression was acute lymphatic leukemia. The patient, feeling perfectly well, again came under observation, Nov 3, 1921, at the request of the physician. At that time the glands before enlarged had receded and were barely palpable. The leukocyte count was 7,000, of which 50 per cent were polymorphonuclear leukocytes. Several examinations later, as shown in the blood chart, showed only slight increase in the relative number of lymphocytes. Seventeen months later the blood count was normal, and only a few small cervical glands were palpable.

The blood findings are given in Table 1. The urine showed a trace of albumin. The Wassermann reaction was negative and the Widal reaction atypical. One blood culture showed no growth.

CASE 2—H. E., a white man, aged 22, single, a student, came under observation, Oct 31, 1921, complaining of sore throat and general aching pains. The

TABLE 3—*Blood Findings in Case 3*

Date	Red Blood Cells	Hemoglobin, per Cent	White Blood Cells	Polymorphonuclears, per Cent	Polymorphonuclear phils, per Cent	Polymorphonuclear phils, per Cent	Lymphocytes, per Cent	Transitionals, per Cent	Large Mononuclears, per Cent
3/ 6/22			22,300						
3/ 7/22				12					
3/ 8/22	5,184,000	90	26,200	25			82	2	4
3/13/22			16,400	31			74		1
3/14/22	4,532,000	90	12,800	27			65	2	2
3/15/22			13,200	33			66	4	3
3/17/22			12,400			1	62	2	2
3/20/22			9,800	39					
3/22/22		85		30	2	1	52	6	3
3/24/22			8,210	32			56	1	10
3/27/22			7,400	31			56	7	5
3/29/22		80	7,800	34		2	57	3	7
6/ 9/22	4,992,000	85	7,000	37	1		48	10	8
							57		5

temperature was 99.6 F. Physical examination showed moderate injection of the throat but no areas of exudate. The cervical, the axillary, epitrochlear and inguinal lymph nodes were all moderately enlarged, but not tender. The spleen was not palpable. There was slight tenderness in the right lower abdominal quadrant. The symptoms cleared up within a few days.

CASE 3—*History*—C. B., a white man, aged 21, single, a student, entered the Students' Health Service Hospital, March 6, 1922, complaining of sore throat and pain in the back. The onset of the present illness was noted on March 1, with sore throat and pain in the lumbar regions. The patient also complained of general aching pains and abdominal discomfort.

*Physical Examination*—This revealed that there was no marked prostration. The tonsils were swollen and covered with patches of grayish-white exudate, which were confluent in some areas. The cervical lymph glands were moderately enlarged, discrete and tender. The axillary, epitrochlear and inguinal glands were likewise moderately enlarged and tender. The spleen and liver were not palpable.

*Course of Disease*—On March 8, jaundice was noted, with slight tenderness along the right costal margin. On March 11, there appeared a brownish erythematous rash over the entire body, which suggested a toxic origin. On March 13, several small petechial hemorrhages were noted in the mucous membranes of the mouth. Within a day the rash over the whole surface of the body became hemorrhagic, within ten days it had largely disappeared. The temperature, which had been of an irregularly intermittent type with a maximum height of 102.4 F, reached normal within six days. The pulse rate averaged around 80.

*Laboratory Findings*—The Wassermann reaction was negative. On March 15, 1922, the throat smear showed a few spirilli and fusiform bacilli. No diphtheria bacilli were found. The feces showed one test negative to guaiac. One blood culture showed no growth. The patient was discharged on March 22. The blood count still showed alteration three months later and the cervical glands were palpable.

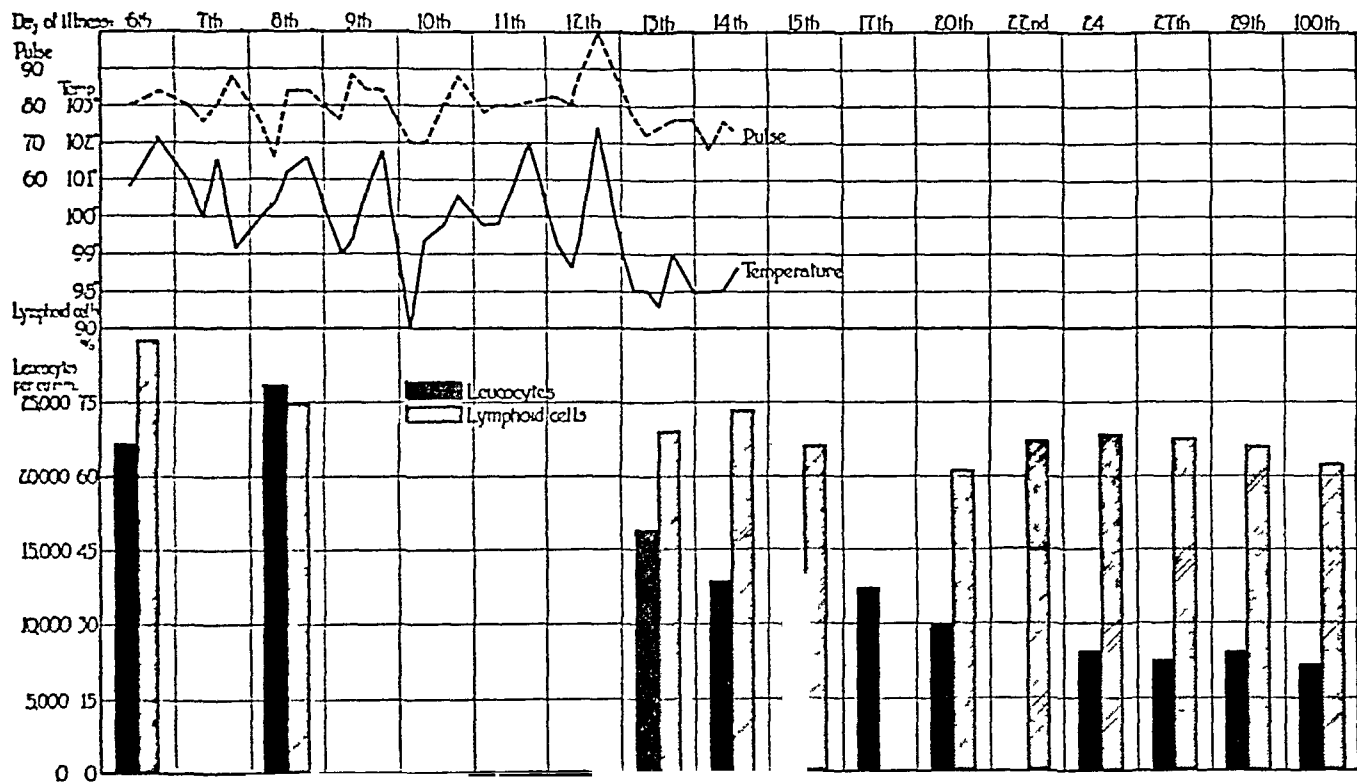


Chart 1—Pulse, temperature, total leukocyte count and percentage of lymphoid cells in Case 3. The leukocyte count is seen to have returned to normal shortly after the fever had subsided, although there was persistence of abnormal percentage of lymphoid cells approximately three months later. The term lymphoid cell is used to describe all forms of leukocytes other than polymorphonuclear types.

**CASE 4**—J. W., a white woman, aged 19, single, a student, entered the Students' Health Service Hospital, April 7, 1922, complaining of slight sore throat and malaise. The onset of the present illness was noted on April 5, with nausea and vertigo. The temperature was then normal. The following day the patient complained of headache and had fever. On the day of admission, sore throat was noted. There were a few scattered whitish patches of exudate on both tonsils, with slight peritonsillar injection. The posterior cervical group of glands, both right and left, were moderately enlarged, discrete, firm and not tender, the anterior cervical axillary and inguinal glands were

palpable but not tender, the liver and spleen were not palpable. The temperature reached a maximum of 103.2 F, and subsided on the eleventh day of illness. One blood culture showed no growth. The patient was discharged on April 17.

TABLE 4—Blood Findings in Case 4

Date	Red Blood Cells	Hemoglobin, per Cent	White Blood Cells	Polymorphonuclears, per Cent	Lymphocytes, per Cent	Transitionals, per Cent	Large Mononuclears, per Cent	Polymorphonuclear basophils, per Cent
4/ 8/22	4,416,000	75	15,400	20	73	4	3	.
4/10/22			26,000	18	77	1	4	
4/11/22			20,600	19	79		2	
4/12/22			14,400	17	77	1	5	
4/13/22			12,650	21	70	4	5	
4/15/22			12,800	19	75	1	5	
4/19/22	4,416,000	80		28	68	2	2	1
4/26/22			8,800	38	54	2	4	
6/ 5/22			8,400	46	45	4	5	

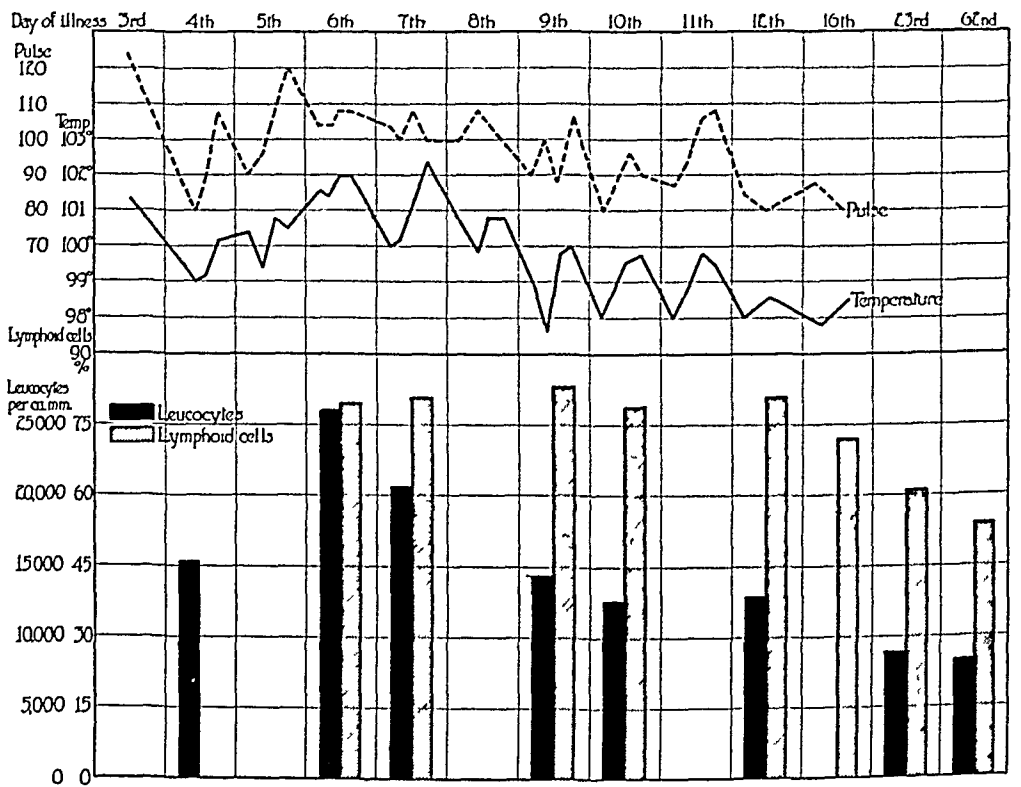


Chart 2—Abnormal percentages of lymphoid cells in Case 4 approximately two months after recovery

CASE 5—A P, a white man, aged 20, single, a student, was admitted to the Students' Health Service Hospital, May 25, 1922, complaining of sore throat. The duration of the present illness was one day. The patient had

sore throat but no other symptoms except slight malaise. Physical examination revealed moderately hypertrophied tonsils. There was a grayish white membrane over the right tonsil, and only moderate peritonsillar injection. The submaxillary glands were markedly enlarged, the left more than the right, and the other cervical glands, as well as the axillary and inguinal glands, were definitely enlarged. The spleen and liver were not palpable. The patient's temperature reached 102.2 F, and pulse rate, 96. Recovery occurred at the end of one week. Laboratory. In a throat smear taken May 27, 1921, spirilli and fusiform bacilli were present, but they were not found in abundance. The patient was discharged on June 1.

TABLE 5—*Blood Findings in Case 5*

Date	Red Blood Cells	Hemoglobin, per Cent	White Blood Cells	Polymorphonuclears, per Cent	Polymorphonuclear Eosinophils, per Cent	Lymphocytes, per Cent	Transitionals, per Cent	Large Mononuclears, per Cent
5/29/22	4,224,000	89	11,660	30	2	56	6	6
5/31/22			10,800	36	3	56	2	3
6/1/22	4,736,000	75	12,400	33	3	59	1	4
6/6/22	4,638,000	75	8,400	37	5	52	2	4
6/12/22	4,742,000	80	8,000	52	2	42	1	3

TABLE 6—*Blood Findings in Case 6*

Date	Red Blood Cells	Hemoglobin per Cent	White Blood Cells	Polymorphonuclears, per Cent	Polymorphonuclear Eosinophils, per Cent	Polymorphonuclear Basophils, per Cent	Small Lymphocytes, per Cent	Large Lymphocytes, per Cent	Transitionals, per Cent	Large Mononuclears, per Cent
12/12/21			6,700	38	1		25	24	5	7
12/15/21			10,700	41			40	15	1	3
12/21/21			9,100	56	1		19	15	4	5

CASE 6—V E, a white man, aged 20, single, a student, entered the Students' Health Service Hospital on December 8, complaining of headache and malaise. The present illness had its onset on Dec 7, with sore throat, headache, malaise and a temperature of 103 F. Physical examination revealed that the throat was reddened but showed no exudate. On December 11, a rash developed, most marked over the chest and abdomen, but present also on the arms, legs and hands. It faded within one day and suggested a toxic origin. Complete recovery occurred within a week. The data are incomplete in this case but those obtained probably warrant its inclusion.

CASE 7—H A W, a white man, aged 36, single, a student, entered the Students' Health Service Hospital, Aug 15, 1922, complaining of malaise, headache and stiff neck. The present illness began on Aug 9, 1922, with the foregoing symptoms. A slight sore throat was also noted, which lasted only over night. Up to the time of entrance, the symptoms had remained about the same. Physical examination revealed palpable anterior and posterior cervical glands, those on the right side were larger, measuring 2.5 cm. The epitrochlear and inguinal glands were also palpable. All the glands were discrete, firm, and not tender. The fauces showed moderate diffuse injection. There was no exudation. The tonsils were adherent. The edge of the spleen was palpable. Table 7 contains the blood count. A roentgenogram of the chest showed no enlarged hilus glands. The urine showed a trace of albumin, no sugar and a negative sediment. Two other specimens showed no albumin.

TABLE 7—*Blood Findings in Case 7*

Date	Red Blood Cells	Hemoglobin, per Cent	White Blood Cells	Polymorphonuclears, per Cent	Polymorphonucle or Eosinophils, per Cent	Lymphocytes, per Cent	Large Mononuclears, per Cent	Transitionals, per Cent	Unclassified
8/15/22	4,042,000	70	12,800	13		77	6	4	
8/16/22			15,600	10	1	81	3	5	
8/17/22		70	15,800	11		78	5	3	
8/19/22	4,564,000	70	21,600	20	2	71	4	3	3
8/21/22	4,042,000	70	14,400	11	1	79	4	3	
8/22/22	4,168,000	70	10,800	19	2	70	6	3	
8/23/22	4,252,000	70	10,000	19	4	65	6	5	1

TABLE 8—*Blood Findings in Case 8*

Date	White Blood Cells	Polymorphonuclears, per Cent	Lymphocytes, per Cent
9/26/22	15,000 •	43	57
10/25/22		61	39

The Widal reaction in the blood was negative. One blood culture showed no growth. A cervical lymph gland was removed, a culture taken, and the gland then sectioned. The culture showed no growth. Microscopic examination showed simple hyperplasia of the type noted in nonsuppurative adenitis. The maximum temperature of 101 F was noted on day of admission. Patient had recovered two weeks after onset. At that time the lymph nodes noted before were still palpable. The patient was discharged on August 24.

CASE 8—E T, a man, aged 21, single, a student, came under observation on Sept 26, 1922, complaining of sore throat and malaise. During the last two months the patient had had frequent sore throats. During the previous week this symptom had been worse and had been accompanied by marked malaise and exhaustion. Physical examination showed throat injection without tonsillar exudate. The interior and posterior cervical, axillary, epitrochlear and inguinal lymph glands were moderately enlarged, but not tender. The spleen was palpable. The temperature was 99.6 F. The symptoms subsided within two weeks. When the patient was seen one month later, the lymph nodes, but not the spleen, were still palpable.

CASE 9—C H, a white man, aged 19, single, a student, entered the Students' Health Service Hospital, Oct 30, 1922, complaining of sore throat and stiffness and swelling of neck. The onset of the present illness occurred, Oct 19, with swelling of the right side of the neck. Four days later the

TABLE 9—*Blood Findings in Case 9*

Date	Red Blood Cells	Hemoglobin, per Cent	White Blood Cells	Polymorphonuclears, per Cent	Polymorphonuclear Eosinophils, per Cent	Polymorphonuclear basophils, per Cent	Small Lymphocytes per Cent	Large Lymphocytes per Cent	Transitionals, per Cent	Large Mononuclears, per Cent	Unclassified
10/30/22	4,350,000	85	11,750	56			23	13	5	3	
11/ 1/22				42.5			40.5	4.5	10		2.5
11/ 2/22			6,150	32			58.5	2.5	5	2	
11/ 3/22				30			40	23.5	5		
11/ 4/22				37		1.5	55.5	2	1.5		2.5
11/ 7/22			5,850	42			46	6	4		
11/ 9/22			9,800	54	0.5	1	35	7.5	1		1.5
11/15/22				78			12	2	3		5

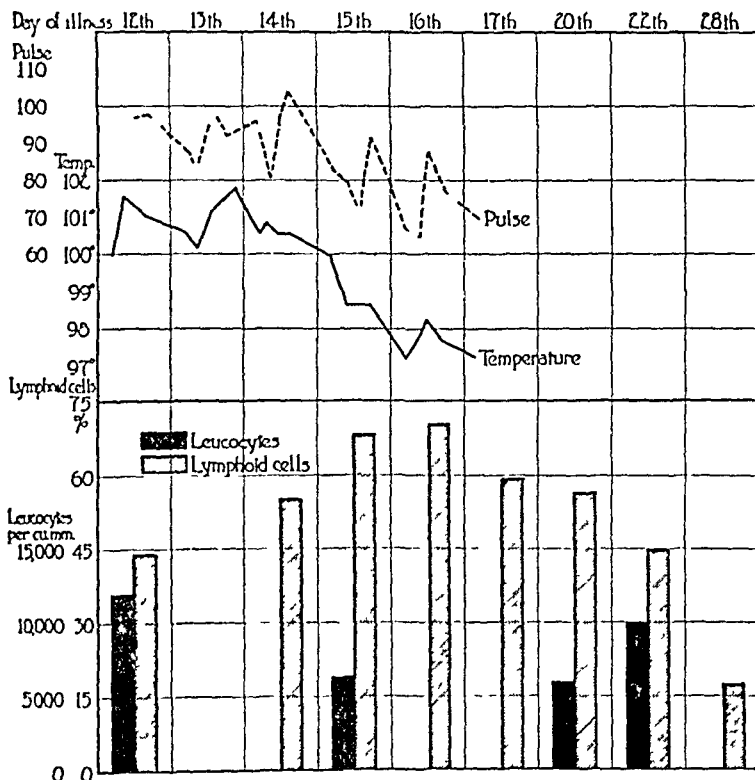


Chart 3—This shows that in Case 9 the maximum percentage of lymphoid cells was reached as the temperature became normal, also the comparatively rapid return of percentage of lymphoid cells to normal.

throat became slightly sore with stiffness of the neck. On being examined on Oct 31, the patient showed no prostration. Both tonsils showed ulcerated areas with only moderate surrounding injection or edema. Anterior and



posterior cervical glands were enlarged, especially the group beneath the sternocleidomastoid muscle, which bulged distinctly in its upper third. The glands were only slightly tender. The surrounding tissues were not inflamed. The axillary and inguinal glands were moderately enlarged, the epitrochlears slightly so. The spleen was readily palpable. Diagnostic impression from clinical findings was acute glandular infection with lymphocytosis. Throat smears gave no predominating organisms. One blood culture was negative. The temperature reached a maximum of 101.8 F, and became normal four days after admission. The throat cleared up during this period. Total duration from the time of the first symptom to the date of normal temperature was fourteen days. The patient was discharged on December 4. He was again seen Nov 9, 1922, when the glands were smaller and the spleen had definitely receded, although it was still palpable. On December 20, the spleen was not palpable.

#### COMMENT

The foregoing patients, eight males and one female, were all young adults. No predisposing factors were present. In all the cases, there was systemic reaction, and the onset was associated with malaise, sore throat and fever. In Case 9, swelling of the neck occurred four days before the throat became sore. In two persons prostration was moderately severe, in the others the course of the disease was mild. Sore throat was the chief complaint through the course of the disease. In five cases, scattered patches of exudate were present on both tonsils. In Case 1, there were also definite ulcerated areas over the tonsils, marked edema and injection of the fauces, with hemorrhages in the buccal mucosae later, and in Cases 3, 5 and 9 also marked inflammatory reaction. The patient in Case 3 developed a purpuric rash, the occurrence of which is of interest in view of the hemorrhages in the mucous membranes and skin common in leukemia. In all other cases, the throat showed only injection without exudation or ulceration. The superficial lymph glands, especially the group in the superior triangle of the neck extending under the sternocleidomastoid muscle, were enlarged (from 2 to 3 cm), the increase being symmetrical in the majority of cases, they were discrete, firm and occasionally slightly tender. The axillary, epitrochlear and inguinal glands were likewise enlarged but rarely tender. In Case 3, while the cervical glands did not show as much enlargement as is mentioned in the foregoing, those in the inguinal region were even greater in size. The periglandular tissue did not show edema, and the marked tenderness sometimes present in acute cervical adenitis was also absent. In all the patients under observation, the glandular enlargement was definite and above the limits seen in normal persons. The spleen was palpable in four persons, the liver in none. In one case a transient jaundice developed. Blood cultures taken in five cases showed no growth.

The blood count in Case 1 showed the greatest variation, there being first a leukopenia with 3,000 white cells, followed by an increase

within six days to 17,200 cells, 81 per cent of which were lymphocytes. As high as 92 per cent of lymphocytes were recorded, therefore an absolute lymphocytosis was present. In the other cases leukocytosis was always present, the maximum counts varying from 10,700 to 26,200, in six cases 15,000 or above. The total percentage of lymphocytes varied from 57 to 92. In all cases, the total leukocyte count approached normal as the defervescence occurred. It is of interest that Cases 1 and 3, with comparatively greater systemic reaction, including the hemorrhages before described, still showed, eight and three months later, respectively, increased percentages of lymphocytes, also that in Cases 1, 3, 4 and 7, with delay in return of lymphocyte percentages to normal, there was persistence of glandular enlargement, although lessened in degree. On the other hand, Cases 5, 6, 8 and 9, with a milder reaction, showed, from fourteen to thirty days after the onset of the illness, a return to approximately the normal percentage of lymphocytes. In Case 9, during a four-day period of defervescence, there was a steady increase in percentage of lymphocytes. One week thereafter, however, 54 per cent of polymorphonuclear leukocytes was reached. Anemia of any marked degree was not observed.

In another series of nine cases with acute throat infections, taken without selection, in which there was no general lymphadenosis and enlargement of the spleen, total leukocyte counts have varied from 11,500 to 17,100, and the polymorphonuclear leukocytes from 74.5 to 89 per cent. This control series in a similar group of young adults has been included to show the dissimilarity between the characteristics of the group of cases here described and of acute tonsillitis and pharyngitis unassociated with the enlargement of lymph glands and spleen.

Although there was considerable variation in the clinical pictures presented, there were certain constant features in all the cases under observation which apparently define a clinical entity. Early in the course of the disease, the tonsils or pharynx, in all cases, showed acute infection as evidenced by areas of exudate and ulceration or by injection alone. This common and early presence of tonsillar and pharyngeal infection commands attention as the most likely portal of entry. The cervical adenopathy was noted first and was most pronounced, as best illustrated in Case 5. In Cases 2 and 8, systemic reaction and pyrexia, although minimal, were definitely associated with acute throat infection. The comparatively low total leukocyte count is of course unusual in leukemia, but is not itself a differentiating sign in the early stages. Hemorrhage into the mucous membranes and skin was observed in two cases, and differed only in its moderate degree from that seen in the leukemia. The anginal throat similar to that of leukemia has likewise been observed.

in two cases. Organisms of Vincent's angina were found in the throats in four cases, the smears, however, showing no marked preponderance of such forms. The throats, with their well developed inflammatory reaction, did not have the appearance characteristic of Vincent's angina. The systemic reaction, also, was out of proportion to that seen in Vincent's angina. In addition, the blood picture in observed cases of true Vincent's angina has never shown marked or constant alteration in percentage of lymphocytes. In view of the presence of the fusiform bacilli and spirilli in diphtheria and other throat infections, apparently little significance can be attached thereto in the cases here observed. The fastigium never extended over three weeks and averaged approximately eleven days. The fever reached a maximum of 103 F, was an irregular, intermittent type, and fell by lysis. The pulse rate increased with the temperature. The patients are all well at present, seventeen months having elapsed since they first came under observation.

The hemorrhagic tendency evidenced in two cases suggests a similarity to leukemia. However, these hemorrhages in the mucosa and skin have not been extensive and have not been associated with anemia. The lymphocytosis of chronic focal infection does not suggest itself in any case.

It is highly important that the benign nature of these cases be recognized and favorable prognosis given. From the standpoint of etiology, emphasis on the resemblance to leukemia should broaden the scope of study.

Dr Downey's study of blood morphology indicates characteristics which separate this group in a similar manner from other pathological conditions associated with lymphocytosis. When taken with the constant clinical characteristics described, a distinct disease entity is apparently defined. From blood findings, prediction of clinical features has been possible, and from clinical features the blood findings. The clinical features of Case 9 were typical and suggested the blood changes afterward reported by Dr Downey. Such features are readily recognized, and always indicate that blood examination is necessary. The usual cases of tonsillitis and pharyngitis have not shown these features and have always been associated with polymorphonuclear leukocytosis.

#### SUMMARY OF CLINICAL STUDY

Certain constant features found in the cases described are (1) the occurrence in young adults of an acute tonsillitis or pharyngitis with systemic reaction, (2) absence of anemia, (3) enlargement of lymphatic glands and frequently of the spleen, (4) lymphocytosis, and (5) the comparatively rapid recovery of the patient.

These features differentiate the group studied from severe infections in which anemia and lymphocytosis have often led to confusion with leukemia. From glandular fever, with its highly epidemic nature, its occurrence in children, and its absence of tonsillitis or marked pharyngitis, differentiation is also clear.

Although many of the symptoms and signs of acute leukemia are present in this group of cases, their moderation, together with the absence of anemia, defines a condition quite dissimilar. None of the cases observed have shown either the progressively malignant course with prostration and anemia, which is usually present in acute leukemia, or the high leukocyte counts, which are also usually present.

These cases, as has been shown, present a distinct clinical entity. In the absence of knowledge of the etiology of the disease, the descriptive term acute lymphadenosis with lymphocytosis is suggested.

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## PART II HEMATOLOGIC STUDIES \*

HAL DOWNEY, PH D

The group of cases described by Dr McKinlay is of special interest to the hematologist first, because it adds another group to the long list of reported cases of infectious disease accompanied by lymphocytosis instead of the usual polymorphonuclear reaction, and second, because numerous authors have had difficulty in distinguishing between the blood picture of such conditions and that of cases of acute leukemia. Prognosis was uncertain in cases reported by some authors, and the diagnosis of acute leukemia has been made by others in cases in which the complete recovery of the patient proved the error. In one of our own cases, the outcome was somewhat in doubt, in spite of the negative blood findings, because the clinical symptoms were similar to those of acute leukemia. In another one of our cases (Case 3), the blood showed some leukemic features, but the clinical findings, with some features of the blood to be mentioned later, would not support a diagnosis of leukemia.

### REVIEW OF THE LITERATURE

Since in only one of the cases of this group (Case 3) and of many other cases of nonleukemic lymphocytosis with other types of infection which have been observed by the writer, were there any blood features

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\*From the Hematological Laboratory, Department of Animal Biology, University of Minnesota. Aided by a grant from the Research Funds of the Graduate School.

suggesting leukemia, it would seem that much of the difficulty in diagnosis has been due to inadequate study of the blood. Perusal of the literature shows this to be the case. With a few notable exceptions, the papers dealing with the subject show little evidence of detailed blood studies. Much attention is given to total counts, percentages, etc., but little to detailed cytology. In most cases, there are no illustrations accompanying the papers, so that it is impossible to pass judgment on the cells described. Lymphoblasts, immature lymphocytes, etc., are mentioned, but often it is impossible to determine the type of cell the authors have in mind when they are thus described. Thus, when it is stated that the blood picture resembled or was identical with that of acute leukemia, the statement must be accepted with some reservation, unless accompanied by descriptive or illustrative proof. Such proof is furnished in the papers of Sprunt and Evans<sup>10</sup> and of Bloedorn and Houghton,<sup>11</sup> and it is evident from their figures and descriptions that there is no danger of confusing the blood picture of such cases with that of acute leukemia.

That a temporary leukemic blood picture, both myelogenous and lymphatic, may accompany infectious diseases of various types is a well known fact (Turk,<sup>14</sup> Naegeli,<sup>1</sup> Roth,<sup>15</sup> Stursberg,<sup>16</sup> Khenenberger,<sup>17</sup> A. Herz,<sup>2</sup> F. Marchand,<sup>18</sup> and many others), and a blood picture which leans more or less toward leukemia has been produced experimentally by Ludke<sup>19</sup> and Pappenheim.<sup>20</sup>

Organ changes more or less similar to those of leukemia, particularly myelogenous leukemia, are known to occur with infectious dis-

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14 Turk, W. Klinische Beobachtungen über das Verhalten des Blutes bei akuten Infektionskrankheiten (Cited from A. Herz) Braumüller, Vienna and Leipzig, 1898. Septische Erkrankungen bei Verkümmerung des Granulocytensystems. Wiener klin. Wchnschr., 1907, No. 6. Vorlesungen über klinische Haematologie. Wien u. Leipzig, Braumüller, 1912.

15 Roth, C. Ueber einen bemerkenswerten Blutbefund bei einem Fall von subakuter Miliartuberkulose (Ein Beitrag zur Frage der akuten myeloischen Leukämie), Ztschr. f. klin. Med., vol. 78, 1913.

16 Stursberg, H. Zur Differentialdiagnose zwischen akuter Leukämie u. Sepsis, mit besonderer Berücksichtigung der "Sepsis bei Verkümmerung des Granulocytensystems," Med. Klin. 8: 520, 1912.

17 Khenenberger. Das Blutbild der akuten Leukämie als passageres Symptom, München med. Wchnschr. 61: 1159, 1914.

18 Marchand, F. Ueber ungewöhnlich starke Lymphocytose im Anschluss an Infektionen, Deutsch. Arch. f. klin. Med., 1913, vol. 110.

19 Ludke, H. Die experimentelle Erzeugung leukämischer Blutbilder, Verh. d. deutsch. Kongr. f. innere Med., 27ster Kongr., Wiesbaden, 1910.

20 Pappenheim, A. Atlas der menschlichen Blutzellen, Jena, G. Fischer, 1905, 1912. Grundriss der hamatologischen Diagnostik und praktischen Blutuntersuchung, Leipzig, Werner Klinkhardt, 1911. Die Zellen der leukämischen Myelose, Jena, G. Fischer, 1914. Haematologische Bestimmungstabellen, Leipzig, Werner Klinkhardt, 1920.

eases, and they have been produced experimentally in various ways by Dominici,<sup>21</sup> Weizberg,<sup>22</sup> Hertz,<sup>23</sup> Isaac and Mockel<sup>24</sup>

Many authors have discussed the intimate relation between acute leukemia and sepsis, and Sternberg<sup>25</sup> claims that acute leukemia is an infectious disease. This view is supported to some extent by Turk, who believes that there is some relationship between what he calls "lymphatic reaction" and lymphatic leukemia. A Herz, basing his opinion on cases of his own and of Turk, concludes that there are cases of general infection in which the blood pictures are identical with those of acute leukemia, both myelogenous and lymphatic, and that the only difference between the two is in the final outcome. He adds that if acute leukemia is an infectious disease, we may assume the existence of a curable form.

Blood pictures which are more or less leukemic in form have also been noted in cases similar to the group reported here. Three of Turk's cases seem to be closely related. They were cases of angina and general infection accompanied by slight swelling of lymph nodes and moderate enlargement of the spleen. The blood picture is described in detail for one of the cases. There were 17,000 leukocytes, with 16 per cent granulocytes. The other cells were partly normal lymphocytes, but mostly atypical, unripe lymphocyte forms.

Naegeli has also had experience with cases similar to those of our group. On page 472, he points out the difficulties in distinguishing between lymphatic leukemia, lymphocytosis and "lymphatic reaction." Severe leukopenia of 800 to 2,000 white cells most of which are lymphocytes is likely to be sepsis with exhaustion or destruction of the marrow. "Lymphatic reaction" causes the greatest difficulty, because the blood shows not only high relative and absolute lymphocyte values, but also atypical lymphocytes and lymphoblasts. But these are usually cases of acute infection with fever, which are soon cured,

21 Dominici, H. Sur l'histologie de la rate a l'état normal et pathologique, Arch de méd expér et d'anat pathol **13**, 1901. Etudes sur le tissu conjonctif et les organes hématopoïétiques des mammifères, Arch d'Anat Microscop **17**, 1921.

22 Werzberg, A. Neue experimentelle Beiträge zur Frage der myeloiden Metaplasie, Virchows Arch f path Anat **204** 272, 1911.

23 Hertz, R. Zur Frage der experimentellen myeloischen Milz-Metaplasie, Ztschr f klin Med **71**, 1910.

24 Isaac, S., and Mockel, K. Ueber experimentelle schwere Anämien durch Saponinsubstanzen, Verh d deutsch Kongr f innere Med, 27ster Kongr, Wiesbaden, 1910, p 471.

25 Sternberg, C. Primärerkrankungen des lymphatischen und hämatopoetischen Apparates, normale und pathologische Morphologie des Blutes, Ergeb d allgem Path u path Anat (Lubarsch-Ostertag), 1905. Ueber die Rolle der Lymphozyten bei den chronischen infektiösen Entzündungen, Verh d deutsch path Gesellsch 16 Tagung, Marburg, 1913.

with the blood gradually returning to normal "For a certain time the diagnosis may be impossible" This condition may be further complicated by a clinical picture which is similar to acute leukemia and is marked by fever, enlarged glands and spleen, and prostration On pages 485 and 486, Naegeli describes several of his own cases and several from the literature which are similar to those of our group In many of his cases, he found large pathologic lymphocytes having a blue staining cytoplasm which reminds one strongly of plasma cells, and on account of these cells Naegeli was able to decide against leukemia in two of the cases He has also noted a somewhat similar blood picture in abdominal typhus, and observed a high lymphocytosis with immature cells in fetal syphilis, which might be diagnosed as myeloblastic leukemia

Cabot's<sup>3</sup> Cases 3 and 4 seem to be similar to those of our group The blood contained 71 per cent and 75 per cent lymphocytes, but from the description of the cells it is evident that the blood picture is not leukemic Nevertheless, Cabot seems to think that there is danger of confusing the picture with leukemia, for he states "The distinction between such a lymphocytosis (accompanying a widespread adenitis) and leukemia depends upon the recognition of an infectious origin for the adenitis, upon the lesser degree of lymphocytosis in the infectious type, and upon the course of the disease"

Other writers see leukemic features in the blood pictures of the cases which they report, although there is nothing about the morphology of the cells to warrant such a conclusion Thus Sanders<sup>4</sup> reports a case of fatal Ludwig's angina in which the blood contained numerous large cells having the morphologic characters of lymphocytes The leukocyte counts ran from 11,000 to 23,000 with 96 per cent lymphocytes, mostly of the larger variety The smears contained cells showing all gradations from small lymphocytes to the large cells having the morphology of lymphocytes In spite of these morphologic characters, Sanders seems to think that he has a blood picture of acute myeloblastic leukemia, for he states "It seemed impossible to conceive that lymphocytes could migrate into the cellular tissues of the floor of the mouth and neck in sufficient numbers to account for the extensive board like swelling We therefore believe that they are the immature histological antecedents of the granular myelocyte, viz, the nongranular myeloblast, and that future studies by the more recent methods will show the leukocytes of the infective lymphocytoses, and most likely the acute lymphoid leukemias to be of myeloid instead of lymphoid origin"

Bloedorn and Houghton<sup>2</sup> describe four cases in young adults which are similar to those of our group The blood picture was

essentially the same in all four cases. The characteristic cells as described and figured seem to be the same as those of one of our types (Type II, Fig 7), but they are described as "lymphoblasts." The authors recognize certain minor differences between the blood in their cases and acute leukemia, but, nevertheless, they seem to be impressed with the difficulty of making a diagnosis, for they state "The differentiation of this type of case from acute lymphatic leukemia may be particularly difficult. The absence of degenerated and fragile cells in the blood smears, the early return of the temperature to normal, the mild course, the absence of hemorrhagic spots and the absence of particularly high leukocyte counts are distinguishing features." None of the cells shown in their figures have any resemblance to the primitive stem cells which are invariably present in acute leukemia. They seem to think that the low total leukocyte counts would distinguish the cases from leukemia, a statement which is hardly in accord with the facts.

Morse,<sup>26</sup> in reporting two cases of "glandular fever" in adults, describes the characteristic cells as "lymphoblasts," but he recognizes the fact that the blood smear is quite different from that of leukemia.

Sprunt and Evans<sup>1</sup> have made a complete blood study on a group of six cases of adults which are identical with those of our group. Their paper is illustrated with a good colored plate, from which, and the unusually complete descriptions, it is evident that the blood picture is in no way related to that of acute leukemia. They believe, however, that differentiation from beginning lymphatic leukemia may be difficult, especially from the clinical side.

Longcope<sup>11</sup> has recently reported a series of ten cases of "infectious mononucleosis," most of which are similar to the cases of our group. The importance of the atypical mononuclear lymphoid cells is realized and they are described in some detail, but there are no illustrations. They are evidently identical with the cells seen in our own cases. Because they do not respond to the oxydase reaction, Longcope believes that they are derived from true lymphoid tissue. He also notes that these cells show no relations to the large mononuclears of normal blood, which corresponds to the findings in our own group of cases.

Longcope recognizes the distinction between these cases and leukemia. After pointing out that they are in no way related to tuberculosis, typhoid fever, Hodgkin's disease and syphilis, he states "The resemblance to leukemia is perhaps most striking, but the early and marked enlargement of the lymph nodes, the absence of anemia and of purpura, and the histological and biological characteristics of



the abnormal mononuclear elements of the blood practically exclude the possibility of considering these cases as instances of mild and transient acute leukemia."

The foregoing outline of certain phases of the literature should be sufficient to indicate the importance of further study of cases of lymphocytosis, particularly of cases accompanied by general adenopathy, like those of our own group, in which the diagnosis has often been uncertain until made clear by the progress of the case. More attention should be given to cytologic studies of the blood with special reference to possible relationships with the leukemic blood picture. It is with the hope of contributing somewhat to this as well as to the clinical side of the question that we are reporting another group of these cases.

#### AUTHOR'S CASES

Among the cases which have come under our observation, three types can be recognized hematologically. These differences are in no way related to leukocyte counts and percentages, but depend solely on the morphologic features of the cells which give the blood its characteristic picture. There is nothing in the clinical findings to warrant such a subdivision of the group, so they are probably of little practical importance, although Type III (Case 3, Figs 8 to 11), which shows some leukemic features, might cause some difficulty in diagnosis, especially if cases occur in which these features are more pronounced than they were in our one case of this type. Each case shows minor variations indicating gradations between the types. This shows that the division of the cases into three types is entirely artificial, nevertheless, it serves to indicate the great difference in the character of the blood picture in the various cases of the group.

Our Type I (Cases 1, 5 and 8, Figs 1 to 6) seems to be the common type, for five of our own cases were of this type, as were also the six cases reported by Sprunt and Evans, some of Naegeli's cases and the four cases of Bloedorn and Houghton. The indistinct half-tone figures accompanying the paper of the latter authors are of cells which look more like the cells of our Type II (Fig 7), but according to the description given, the cells are more like those of our Type I. The colored plate published by Sprunt and Evans shows that their cases were identical with our Case 1. Their cells 3, 4, 5 and 7 look as though they had been taken from our case.

These authors state that the blood picture in the five cases observed from the beginning was the same, showing practically no variations. Bloedorn and Houghton also noted little variation in the blood picture of their four cases. Naegeli's cases showed considerable variation in

the blood picture, some were of the leukemic type, while others clearly belong to our Type I (Figs 1 to 6)

Our Case 1 will be described in some detail, because this case showed many of the clinical features of acute leukemia and was so diagnosed in spite of the negative blood findings. The negative blood report was based on the morphology of the cells and not on the counts. The first leukocyte count on March 6, 1921, gave a total of 3,000 with 83 per cent lymphocytes. Five days later, the total count had gone up to 17,000 with 92 per cent lymphocytes. Such counts are common in acute leukemia, and are practically identical with the counts obtained in a case of acute lymphatic leukemia which we have illustrated with Figures 12, 13 and 14 of our plate in order to compare the cytology of acute leukemia with that of benign lymphocytosis.

Typical cells from our Case 1 are illustrated in Figures 1 to 6. They are not excessively large cells, as can be seen by comparison with the other figures of the plate which are all drawn to scale by outlining with the camera lucida at the same magnification. When compared with the lymphoid cells of normal blood, it is seen that they are all atypical, pathologic forms, including even the medium-sized lymphocyte of Figure 4, which has a more basophilic and vacuolated cytoplasm than is usual for these cells.

Nearly all of the lymphoid cells of this blood when first examined were atypical to the extent illustrated in the figures. In spite of the marked lobulation of the nuclei of many of the cells, which is quite characteristic for this particular case, it is evident that all of the cells belong to the lymphocyte series, for it is possible to select a complete series of transition stages leading from a lymphocyte like the one shown in Figure 4 to the large cells of Figures 1, 2, 3 and 5.

In building up a series of this kind, particular attention must be given to the inner nuclear structure. The size and form of the nucleus are of little value in determining genetic relationships or stage of differentiation of the cells, but the quantity and distribution of chromatin and its relation to the parachromatin is of great importance. This is a principle which has been emphasized time and again by Pappenheim and which is now universally recognized by hematologists who are working on the pathologic side of blood. Pappenheim believes that the form of the nucleus and its relative size determine the age of the cell at any particular stage of differentiation.

According to this scheme, a wide-bodied cell having a nucleus with inner structure similar to that of Figure 13, but lobulated like those of Figures 1, 2 or 5 would be an older, "leukocytoid" lymphoidocyte (myeloblast of Naegeli), while cells having the inner nuclear structure of lymphocytes, but with lobulated nuclei surrounded by a wide cell

body would be older, leukocytoid lymphocytes. In other words, it is quite possible to distinguish between morphologic characters which are due to immaturity and lack of differentiation and those which are due to the process of "aging" and further differentiation.

Perusal of the literature on lymphocytosis shows that these principles must be kept more clearly in mind when studying this condition, and especially when it is desired to compare it with true leukemia. We find that the terms "lymphoblast," "germ center cell," "immature cell," etc., have been used in cases that did not justify such terminology, and this is undoubtedly partly responsible for the prevailing opinion that it is difficult to distinguish hematologically between these cases of benign lymphocytosis and acute leukemia. That there may be real difficulty in some cases has already been admitted, but this is certainly not true of the average case, as we hope to show by this report.

Applying these principles to the cells of our Case 1, it is readily seen that the characteristic cells are highly differentiated, mature, "leukocytoid" lymphocytes, rather than immature "lymphoblasts." The lymphocyte type of nucleus is seen in all of them, although it may be slightly modified in the largest cells (Figs 2 and 3), which have probably been derived from large "mesolymphocytes."

Figures 4 and 5 are best for the characteristic structure of the lymphocyte nucleus. The chromatin forms a coarse network of heavy strands and masses which are not sharply separated from the parachromatin. This gives the nucleus a cloudy appearance which is quite characteristic for the lymphocyte. In some cells there is a slight condensation of the chromatin with corresponding separation from the parachromatin, resulting in the formation of a more definite network (Fig 1). The dense rounded or angular blocks of chromatin characteristic of the nuclei of plasma cells, of which there are a few in this blood, are the result of further condensation. The plasma cell nuclei are somewhat similar to the nucleus of Figure 7, which is from another case.

In some of the larger cells, there may be a slight tendency toward a more diffuse arrangement of the chromatin (Fig 2), but this is never sufficient to warrant classification of the cell as a lymphoblast or particularly immature cell, because the lymphocytic nature of the nucleus always remains evident. The difference is immediately apparent if Figure 2 is compared with the immature lymphocytes of a case of acute lymphatic leukemia shown in Figures 12, 13 and 14. Figure 13 is the most immature cell of this series, and it is identical with the "myeloblast" of Naegeli. It is followed by the older cells shown in Figures 14 and 12, which illustrate the gradual differentiation of the lymphocyte from the "stem-cell." These cells are characterized by the



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4



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8



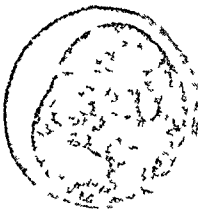
9



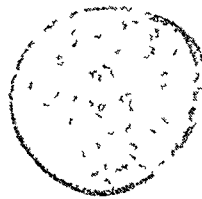
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11



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13



14

CEY

#### EXPLANATION OF PLATE

All the figures are drawn with the same magnification (Zeiss 2 mm apochromatic objective, N A 1.4 and compensating ocular 8) and outlined with the camera lucida, drawing board at the height of the stage

Figs 1-6—The predominating types of lymphoid cells in Case 1. The clinical picture of this case was almost similar to that of acute leukemia, but the blood contained no immature cells. The predominating cells of Cases 5, 6, 8 and 9 were almost similar to these. They and Case 1 are grouped as Type I.

Fig 7—The characteristic cell of Type II, which includes Cases 2, 4 and 7, and one case reported by Dr Cross. The nuclei of these cells frequently resemble those of plasma cells derived from lymphocytes. The cytoplasm is not so basophilic and not so vacuolated as in Type I.

Figs 8-11—Cells from Type III, Case 3. In general, the cells from this case resemble those of Type I, but some of them show leukemic features, such as the azurophilic rod in the large vacuole of Figure 11, narrow bodied cells with indented nuclei (not illustrated), and cells with nuclei which are more or less immature, i. e., with diffuse sievelike arrangement of chromatin and nucleoli (Figs 8 and 9).

Figs 12-14—Immature cells from a case of acute lymphatic leukemia. These are included in order to facilitate comparison of benign lymphocytosis with acute lymphatic leukemia. The total count and lymphocyte percentage in this case were similar to the counts in Case 1 (Figs 1 to 6).



extremely fine and regular chromatin network, the presence of nucleoli, and the abundant and distinct parachromatin which seems to be composed of innumerable fine, rounded granules embedded in a continuous mass of chromatin. This "leptochromatic" structure is seen best in cell 13, while cells 14 and 12 show how the nuclear structure gradually becomes coarser ("pachychromatic"—Pappenheim) with progressive differentiation.

The three cells just referred to show all of the morphologic signs of immaturity and lack of differentiation, while the cells of our Case 1 (Figs 1 to 6) are highly differentiated, mature and functionally active cells. Their state of differentiation is read from the inner structure of the nucleus, indicating mature lymphocytes in this case, while the age of the cells and their functional activity are expressed by the lobulation of the nucleus, the vacuolization of the cytoplasm, the large amount of hyaloplasm and the azure granules. Signs of aging and functional activity may also be seen in immature cells, such as the one illustrated in Figure 14, which is a cell having a nucleus close to that of the stem-cell, but with a wide cell body.

The foregoing is the explanation which Pappenheim<sup>17</sup> gives for the varying morphology of the lymphoid cells. It may or may not be the complete explanation of the underlying causes of morphologic variability of the cells, but nevertheless it serves the purpose of enabling us to draw a sharp line between cytologic characters due to immaturity and those which are due to some other cause. There were no immature cells in our Case 1.

The nuclei of the larger cells are frequently placed eccentrically and are generally lobulated or indented, as shown in the illustrations. Many of the smaller cells also have irregular nuclei (Fig 6). There is an occasional cell with a very wide and pale cell body consisting mostly of hyaloplasm, but with the nucleus of a mesolymphocyte. A few of the larger types of cells have nuclei which nearly fill the cell, and these large nuclei may be irregular in outline.

The cytoplasm in the predominating type of cell of all of the cases of Type I is quite characteristic. The degree of basophilia varies somewhat, but most of the cells are very basophilic, much more so than is usual in the normal large lymphocyte or large mononuclear. There is an occasional cell with the nuclear and cytoplasmic characters of a plasma cell, but most of them do not have the nuclear structure of plasma cells, although their spongioplasm may be just as basophilic. With Wright's stain the spongioplasm appears as dark blue or slate blue, finely granular or flaky, material with a pale yellowish background of hyaloplasm. Its distribution is such that it gives the cytoplasm a vacuolated, foamy or mottled appearance. The peripheral

portion of the cell may contain relatively more spongioplasm and therefore appear darker and more homogeneous than other parts of the cytoplasm. If the nucleus is indented, as is frequently the case, the cytoplasm in the neighborhood of the indentation contains relatively more of the yellowish hyaloplasm and is, therefore, lighter than the rest of the cell.

Frequently (Case 1) there are one or more azurophil granules embedded in the hyaloplasm of this region, which give the whole structure the appearance of a centrosphere. Most of the atypical cells contain azurophil granules, and they are quite abundant in most of the larger cells. They are usually of the lymphocytic type, i. e., fine and carmin red. There are a few cells with large spherical granules. Variations were noted in the number and size of the azure granules and in the number of cells containing the granulation in the different cases of Type I. These will be referred to more specifically in the notes on these cases.

The blood picture of Case 1 returned slowly to normal, although the patient was clinically well three months after the onset of the disease. After eight months, the total number of leukocytes was normal, but 50 per cent of them were lymphocytes with a few of the atypical forms. Eleven months after the beginning of the illness, the atypical cells had disappeared, but the differential count still showed 50 per cent lymphocytes with a normal total leukocyte count.

In order to avoid needless repetition, the other cases of Type I (Cases 5, 6, 8 and 9) will be described in the form of brief notes comparing the cases with Case 1.

#### TYPE I CASES

CASE 5—The atypical cells are not so basophilic and there are not so many with lobulated nuclei as in Case 1 although cells with eccentric nuclei are quite numerous. Their nuclear structure shows that they are modified lymphocytes. A few of them contain nucleoli, but these are surrounded by heavy masses of chromatin, so that the nucleus still preserves its lymphocytic character. There are no other signs of nuclear immaturity. The cytoplasm is spongy and vacuolated and it rarely contains azure granules. There are a few basophilic monocytes with greatly lobulated nuclei and cytoplasm loaded with fine azurophil granules. These may be mistaken for neutrophilic myelocytes if the cytologic analysis is not made with sufficient care. Similar cells were not seen in Case 1. Most of the atypical cells had disappeared eight days after the first examination.

CASE 6—Large and medium-sized atypical lymphocytes similar to those of Case 1 are present, but there are not so many large cells, the lobulation of the nucleus is not so extreme, the cell-body is not so wide, and the azure granulation is rather coarse. Cytoplasmic vacuoles are present and the spongioplasm is basophilic. There are many more normal small and medium-sized lymphocytes than in Case 1. A small percentage of neutrophilic metamyelocytes was noted.

CASE 8—The atypical cells are similar to those of Case 1, except that the nuclei are not so lobulated. Azure granules are present in most of the cells, including the very basophilic ones. This case contains more cells of the monocyte type with lighter, lobulated nuclei and abundant fine azure granulation in the cytoplasm. The nuclei of these cells do not show the coarse chromatin strands seen in the lymphocytic type of cell (the atypical cell characteristic of the disease).

CASE 9—Case 9 is practically identical with Case 1, except that the azure granulation is not found in so many cells and is finer than in the cells of Case 1. Some of the plasma cells have rather diffuse nuclei which gives them a structure approaching that of the Turk irritation form.

#### TYPE II CASES

The next series of cases belonging to the group reported here are those included in our Type II. They include Cases 2, 4 and 7, and one outside case, already reported by Dr J. G. Cross,<sup>12</sup> which we were permitted to study.

All of the cases of this series have a strikingly similar blood picture, which is characterized by the presence of atypical cells having a different morphology from those of Type I. There are slight gradations between the extremes of the two types, so it is likely that these morphologic characters are of slight importance.

An atypical cell of this series is illustrated in Figure 7, which represents the characteristic cell of Case 4. The slight variations from this type seen in the other cases will be pointed out in the notes on those cases.

The nucleus of Figure 7 is somewhat similar to that of a plasma cell. The chromatin strands are very coarse, and there are several dense, rounded or angular masses of chromatin among them. The arrangement of chromatin in dense masses is quite characteristic of the nuclei of plasma cells derived from lymphocytes, and the nuclei of many of the atypical cells of this series approach the plasma cell type more or less. They have more of a washed appearance, and the blocking of the chromatin is not so pronounced as in the plasma cell, but it may be more evident than is the case in Figure 7.

These considerations alone indicate that the cell of Figure 7 should be classified with the lymphocytes, and this conclusion is supported further by the fact that in all of the cases it is possible to build up a complete series of intermediate stages between the larger and medium-sized lymphocytes and the atypical cells having lymphocyte or plasma cell nuclei.

The cytoplasm in this series (Fig. 7) is very different from that of the cases belonging to Type I (Figs. 1 to 6). It has fewer vacuoles and its spongionoplasm has a smoother appearance which does not give the foamy, spongy and stippled effect noted in the cells of Type I. It is generally less basophilic, and there is a more even mixing of spongionoplasm and hyaloplasm. Figure 7 illustrates the tendency of the basophilic portion of the cytoplasm to be arranged in the form of broad bands radiating from the nucleus. This arrangement was striking in many of the cells of Case 4, but was not noted in the other cases of the series.

The cell body is generally wider than in the cells of Type I, and the nucleus is rarely lobulated. In Case 4, the nucleus seems to be quite fragile, for in most of the cells it is damaged somewhat and is generally squeezed out to one margin of the cell. This occurs in many different slides, so the damage is probably not due to the manner in which the smear was made.

Case 4 contains about a normal percentage of large mononuclears with lobulated nuclei and fine azurophil granulation in the cytoplasm.

Cases 2 and 7 are also of Type II, as is also the case reported by Dr. Cross.

CASE 2—The atypical lymphocytes are practically identical with those of Case 4, except that there are more cells with narrow cytoplasm. There are few normal small or medium-sized lymphocytes, although one sees an occa-



sional medium-sized lymphocyte with a very narrow cell body but with a mature nucleus. There are no immature cells. The cytoplasm of the atypical cells is pale as shown in Figure 7, but contains irregular basophilic areas in place of the basophilic streamers radiating from the nucleus. There are few cells with azurophil granules, those with granules contain from 1 to 3 of them. A few monocytes with lobulated or indented nuclei and fine azure dust in the cytoplasm, and transitional stages between these and the large lymphocytes are present. Eighteen days after the first examination, the atypical cells had practically disappeared from the blood. In this respect the case differs markedly from Case 1.

CASE 7—The atypical cell is a large wide-bodied cell with the nucleus of a medium-sized lymphocyte. The cytoplasm contains cloudy, basophilic areas which, however, do not radiate from the nucleus as in Figure 7. There are large vacuoles in the cytoplasm of some of the cells, and some cells contain very large, round azurophil granules. Cells with lobulated nuclei are scarce. An occasional atypical cell was found whose nucleus contained one or more nucleoli. But this was the only sign of immaturity, for in other respects the nucleus was that of the ordinary medium-sized lymphocyte. There are a few normal small and medium-sized lymphocytes and all transitional stages between them and the atypical large cells. These transitional stages are so numerous that there is no question in this case that the atypical cells are derived from lymphocytes.

Another case which we were permitted to study belongs in this series. It is the case reported by Dr. Cross as Case I of his series. The blood picture is almost similar to that of our Case 4 and the atypical cells are like the one shown in Figure 7, except that the cloudy basophilic areas do not radiate from the nucleus. The nucleus of a great many of the cells is very much like that of Figure 7. The chromatin blocks are distinct, and in many of the cells the nuclei are of the plasma cell type, although the cytoplasm is not like that of a plasma cell. Few of the nuclei are lobulated, and there are not many vacuoles in the cytoplasm. None of the nuclei show signs of immaturity, so the blood picture does not suggest leukemia.

#### COMMENT

All of the cases of our Types I and II are characterized by the presence of atypical cells which are clearly modified lymphocytes, or mesolymphocytes of Pappenheim. The abnormal characters are due to greater maturity and functional activity of the cells. Only occasionally are signs of immaturity present, and then they are never sufficient to confuse the picture with that of leukemia. Such signs were noted in Cases 2, 4, 5 and 7. In Case 2 there was an occasional medium-sized lymphocyte with a very narrow cell-body, but with mature nucleus. Case 4 was marked by extreme fragility of the pachychromatic (coarse structured) nucleus. In Cases 5 and 7, there were a few cells with nucleoli in an otherwise normal lymphocytic nucleus. Case 9 had a few plasma cells approaching the Turk irritation form, that is, with leptochromatic nuclei.

#### TYPE III CASES

Our Type III includes cases showing more leukemic features than any of those described under Types I and II. We have only one case (Case 3) to report under this heading. This case is also marked by

the presence of rather large atypical cells which in general are somewhat similar to those of Case 1 (Figs 1 to 6). The cytoplasm is vacuolated and in some cells it is quite basophilic (Fig 10). In the larger cells (Figs 8 and 9), there is usually relatively more hyaloplasm, but the distribution of the spongioplasm remains about the same, in which respect the case differs markedly from those of Type II (Fig 7).

The leukemic features are of chief interest in this case. Possibly 1 per cent of the lymphoid cells contain a single large vacuole with an azurophil rod, in addition to smaller vacuoles distributed rather evenly throughout the cytoplasm. The larger vacuole is located within an indentation of the nucleus. One such cell is illustrated in Fig 11, from which it is seen that the nucleus is that of a typical mesolymphocyte. Azurophil rods or fibers located in large vacuoles are features which have been reported in many cases of acute leukemia, especially in those of the lymphoidcytic (myeloblastic) type.

The nuclei of some of the atypical cells are dedifferentiated to such an extent that some of them closely approximate the lymphoidcytic type. Figure 8 is one such cell with a diffuse, vacuolated nucleus having three nucleoli. Comparison of this cell with those of Figures 12, 13 and 14 from a case of acute lymphatic leukemia shows that its nucleus is close to that of the stem-cell. It resembles closely the nuclei of Figures 12 and 14.

The smears contain numerous intermediate stages leading from the cell with immature nucleus to cells having nuclei like the one of Figure 11, which is a typical, completely differentiated lymphocyte nucleus. In the series which we have illustrated, the nuclei of Figures 9 and 10 are intermediate between those of Figures 8 and 11.

An occasional neutrophilic myelocyte was found in the blood of this patient and also a small number of medium and small lymphocytes with very narrow cell-bodies and indented or slightly lobulated nuclei.

The clinical features of this case were clearly against leukemia. The hematologic report was also negative for leukemia on account of the small number of immature cells and the presence of numerous lymphocytic plasma cells. These are cells with nuclei having coarse, distinct blocks of chromatin, a character which is usually pronounced in plasma cells derived from lymphocytes. These cells may occur in lymphatic leukemia (Naegeli), but they are usually not numerous. The Turk irritation form of plasma cell with diffuse myeloblastic nucleus may be abundant in various forms of leukemia, especially in those of the myelogenous type.

Naegeli was also able to decide against leukemia in two of his cases on account of the numerous plasma cells present. But Naegeli warns against the assumption that the presence of a few plasma cells excludes leukemia.

Sternberg<sup>18</sup> states that plasma cells do not occur in chronic leukemia, except where there is a coexisting inflammatory process. They do occur in acute leukemia, and this is one of Sternberg's reasons for believing that acute leukemia is an infectious process and not a true leukemia. He says that in chronic lymphatic leukemia plasma cells may be found separate from the leukemic infiltrations, especially in association with ulcerative processes.

In our own case (Case 3), there were not enough immature cells to suggest acute leukemia, while the sudden onset of the disease and the clinical findings, together with the occurrence of plasma cells in the blood were against chronic lymphatic leukemia.

#### DIFFERENTIAL DIAGNOSIS

Although the blood picture varies considerably in the three types of cases which we have reported, it has been shown that there are certain characteristic features which distinguish them from acute leukemia. This is true even in Case 3, in which the leukemic features were more pronounced than in the other cases. In this case, as in all the others, there are predominating atypical lymphocytes which give the blood its special character.

The morphologic features which characterize the atypical cells are largely cytoplasmic, but the nucleus may also be involved, as is shown by those cases in which the nucleus approaches the plasma cell type. In Case 3, we see that decidedly immature lymphocytes with leptochromatic nuclei and nucleoli may show cytoplasmic characters similar to those of the atypical cells derived from fully differentiated mesolymphocytes.

The atypical cells show some plasma cell characters which are more pronounced in some cases than in others. They may, therefore, be described as "abortive plasma cells." They are different from those seen in acute forms of leukemia, which are usually of the Turk irritation form.

In addition to the "abortive plasma cells," there may be other atypical cells, few in number, but with some leukemic characters. They and cells with immature leptochromatic nuclei are more abundant in acute leukemia than they were in any of our cases.

As far as the blood is concerned, there may be greater danger of confusing some of our cases with chronic leukemia than with the acute form. We have one good example of this possibility in a case of chronic lymphatic leukemia which is now under daily observation. The total count in this case has varied between 27,000 and 62,000, with the usual high percentage of lymphocytes. There are few immature cells, and on certain days the majority of the cells are of the type

shown in our Figure 7. The history, clinical findings and rapid changes in the cytology of the blood serve to distinguish this case from those in the group which we are reporting. On the other hand, the special characters of the cells which we have called atypical cells or abortive plasma cells, the small number of immature cells and cells showing other leukemic features, as well as the clinical findings, differentiate our cases from acute leukemia.

Total leukocyte counts and differential counts which do not distinguish between the different types of lymphoid cells present are of little value in deciding for or against acute leukemia.

One of our own cases and two outside cases referred to the writer for hematologic diagnosis may be cited in support of this statement. In spite of the fact that the total leukocyte count and the percentage of lymphocytes were about the same in the three cases, they represent three different types of disease. Although the counts were similar, the cytology was different in the three cases. Both the clinical findings and the counts pointed toward acute leukemia, which was suspected in all of these cases. Study of the blood cytology, however, showed only one of them to be leukemic. This checked with the final outcome of the cases.

The first case is our Case 1 (Figs 1 to 6) which has already been described in detail. When the blood was first examined soon after the onset of the disease, there were 3,000 leukocytes with 83 per cent lymphocytes. Five days later there were 92 per cent lymphocytes. That these were not of the leukemic type has already been shown.

The next case was one of mouth infection with fever and extensive ulceration of the mouth and tongue. Smears from the ulcers contained Vincent's organisms. There were 3,200 leukocytes with 85 per cent lymphocytes. Twelve days later, the total count had dropped to 2,600 leukocytes and 92 per cent lymphocytes.

Cytologic study showed that the case was not leukemic and that it did not belong with our group of nine cases of benign lymphocytosis. There were a few atypical monocytes, but the lymphocytes were normal, except for an occasional large leukocytoid form somewhat similar to the one shown in our Figure 7, but without the cloudy areas. The azurophil granulation when present was normal. There were no immature cells. Large and medium-sized lymphocytes predominated, but there were a few small ones. The patient made a complete recovery and the blood returned to normal in about one month.

The third case with a similar total count and percentage of lymphoid cells was one of acute lymphatic leukemia. The case ran a clinical course typical for that disease and diagnosis was confirmed by histologic examination of the organs.

The first differential count in this case gave 84 per cent lymphocytes with a total leukocyte count of 3,200. The total count fluctuated between 3,000 and 5,000 for the next six days and began to rise on the seventh day, reaching 17,500 on the tenth day, which was the day before death. The percentage of lymphocytes gradually increased until it reached 99 per cent the day before death.

Clinically, there was little to distinguish this case from the case of mouth infection discussed above, except that there was less ulceration in this case. The swollen and sore gums were at first ascribed to Vincent's gingivitis and pyorrhea. Leukocyte counts were similar in both cases when first seen, and anemia was not pronounced in either case. In the leukemic case, there were three million red cells and 70 per cent hemoglobin the day before death.

The blood cytology of the leukemic case was totally different from that of either of the other two, showing a low total leukocyte count. This blood contained great numbers of atypical lymphoid cells in which the abnormal morphology was clearly due to immaturity and lack of differentiation. The number of such cells increased steadily with the progress of the disease until finally 85 per cent of the lymphoid cells were immature lymphocytes.

We have illustrated three cells from this case in Figures 12 to 14. Figure 13 is probably the most immature cell of the three, but Figures 12 and 14 are close to the stem-cell. Comparison of these cells with those of Figures 1 to 6 from our Case 1 will immediately show the difference between morphologic changes due to immaturity and those due to other causes.

The blood of this leukemic case is of special interest and importance, because it contains all the intermediate stages between cells similar to the myeloblast of Naegeli and normal, fully differentiated lymphocytes. Discussion of this case, however, is reserved for a later paper, when the case will be reported in detail. For literature on cases of similar hematologic importance from the standpoint of the monophyletic theory of blood cell relationships, the reader is referred to the papers by Fineman,<sup>27</sup> Citron<sup>28</sup> and Du Toit<sup>29</sup>.

These three cases furnish a good illustration of the fact that the terms "lymphoblast" and "germ center cell," which have been used in the descriptions of benign lymphocytosis with adenoid hyperplasia, should be used with caution. The term "lymphoblast" may be justi-

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27 Fineman, S. A Study of Microlymphoidocytic Leukemia, *Arch Int Med* **29** 168 (Feb) 1922.

28 Citron, J. Ueber zwei bemerkenswerte Falle von (akuter) Leukämie, *Folia Haematol*, *Arch* **20** 1 1915.

29 Du Toit, P. J. Beitrag zur Morphologie des normalen und des leukämischen Rinderblutes, *Folia Haematol* *Arch* **21** 1, 1916.

fied for cells like those shown in Figures 12 to 14, or even for a cell like that of Figure 8, if by lymphoblast is meant a cell whose nuclear structure indicates immaturity or lack of differentiation. Such cells, however, are not the type found in the germ centers of normal lymph nodes, and they are not necessarily the mother cells of the lymphocytes. They are abundant in acute leukemias, although the dedifferentiation does not necessarily reach back as far as the cells of Figures 12 to 14.

The finding of an occasional immature cell, as in our Case 3 (Figures 8 and 9) does not warrant a diagnosis of acute leukemia, even though the clinical picture should point in that direction. In chronic lymphatic leukemia there may be few immature cells, so that the diagnosis of that condition will frequently have to depend on other findings.

A lymph node was obtained from one of our cases (Case 7). In structure it seems to be similar to the nodes described by Sprunt and Evans, who removed nodes from three of their cases and found them to be very hyperplastic with some obliteration of structure. They differed from leukemic nodes only in the degree of hyperplasia.

The node from our case was hyperplastic, but showed small remains of follicles at the periphery. The peripheral sinuses were comparatively free, and there was no invasion of the capsule. The interior of the node was quite diffuse, with large areas of extremely small lymphocytes. Scattered here and there through the node, there were groups or single large lymphocytes with extremely basophilic cytoplasm, thin nuclear membranes, little chromatin and prominent nucleoli. These must be regarded as immature lymphocytes. The atypical lymphocytes of the blood could not be recognized, which seems to indicate that the atypical characters are assumed after the cells reach the blood.

The proliferation of the reticulum of the medullary sinuses noted by Longcope in the nodes of two of his cases was not seen in our case.

Comparison of this node with one from a case of chronic lymphatic leukemia shows only slight differences. The leukemic node shows some large germ centers, but no definite follicles, the peripheral sinuses are filled with lymphocytes, and there is slight invasion of the capsule. The distinct areas composed of extremely small lymphocytes are lacking in the leukemic node. In other respects, the two nodes are almost similar.

#### SUMMARY OF BLOOD STUDIES

Cytologic study of the blood in nine cases of benign lymphocytosis accompanied by adenoid hyperplasia has shown that the blood picture is sufficiently characteristic to warrant inclusion of all of the cases in one large group. The blood is characterized by the presence of a rela-

tively large number of atypical "leukocytoid" lymphocytes, which show sufficient variation in structure to suggest division of the cases into three types. The abnormal cell characters may be interpreted as being due to higher differentiation and special cell activity. In one case, these characters were combined with the nuclear signs of immaturity in a few cells. The blood of this case contained some other leukemic features, but they were not sufficient to warrant a diagnosis of acute leukemia.

Special attention was given to comparison of these specimens of blood with the blood picture in acute leukemia. In every case, it was possible to determine the nonleukemic nature of the blood, even though the clinical picture suggested acute leukemia.

A detailed comparison was made between one of these cases and one case of acute lymphatic leukemia having a total leukocyte count and lymphocyte percentage similar to our Case 1. A case of mouth infection with similar counts is described, and it is shown that the blood cytology is totally different from that of the leukemic case and from the group of cases of benign lymphocytosis. All three cases showed clinical symptoms of acute leukemia, but the blood picture differed in each case, and was sufficiently characteristic to permit correct diagnosis.

# THREE FATAL ADULT CASES OF MALABSORPTION OF FAT

WITH EMACIATION AND ANEMIA, AND IN TWO ACIDOSIS  
AND TETANY \*

HERRMANN L. BLUMGART, M.D.  
BOSTON

The first step toward the treatment of a disease is the recognition of its existence. In the last seven years at the Peter Bent Brigham Hospital, there have been three cases which were not in accord with any hitherto recognized diagnosis, and which, because of the similar signs, symptoms, course and postmortem findings, strongly suggested a definite disease entity. Study of these cases has yielded little knowledge of the underlying etiologic factors. Because of this fact, these cases are presented, in the hope that similar cases will be more easily recognized, and more fruitful effort result.

## REPORT OF CASES

**CASE 1—History**—A. J. N., aged 42, married, a piano-case maker, entered Peter Bent Brigham Hospital, Dec. 20, 1916, complaining of weakness and gaseous distension of the abdomen. His family, marital, and past history presented no significant data. His habits were excellent. He was born in Sweden, and had lived in Boston for twenty-five years. He had usually enjoyed good health. His illness dated from one and one-half years before admission, when, without evident cause, he had suffered from watery diarrhea. The stools numbered from four to five daily and never contained macroscopic blood. At the onset of the diarrhea, he was troubled by considerable epigastric distention, "sour stomach," and borborygmus. The diarrhea ceased after four months, but the gaseous distention persisted. He continued to work, but tired more easily.

Six weeks previous to entrance, he became noticeably short of breath, and observed that his feet swelled occasionally. Three weeks previously, along with a continuation of his dyspnea, he became increasingly weak, and, one week before coming to the hospital, was finally forced to stop work. The appetite was excellent, the bowels moved once a day, and he suffered no pain.

**Physical Examination**—The patient was well developed, but thin. He lay quietly in bed, in no evident pain or discomfort. The face was somewhat emaciated, and there were several areas of vitiligo about the chin and throat. The skin was slightly yellow, pale and dry. The lips were pale, the tongue smooth, slightly reddened and shiny. The heart was normal, the rate, 80 per minute. Systolic blood pressure was 98, diastolic, 40. Physical examination of the lungs was negative save for a few dry râles at the right base, and a harsh expiratory grunt audible over all the front and back. The abdomen was rather full and distended, and tympanitic throughout. There were no masses, or areas of spasm or tenderness. The reflexes of the arms and legs were normal. Moderate soft edema was evident over both ankles. Ophthalmoscopic examination showed normal fundi. The temperature, respiration and pulse were normal.

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\* From the Medical Clinic of the Peter Bent Brigham Hospital.



*Laboratory Findings*—Nine complete blood examinations during the patient's forty-nine day stay in the hospital showed the hemoglobin to average 73 per cent, the red blood count, 2,900,000, the white blood count, 5,000. The differential count averaged polymorphonuclears, 65 per cent, lymphocytes, 30 per cent, transitional cells, 5 per cent. There were no eosinophils, mast cells or myelocytes. The red blood cells showed considerable variation in size, with many microcytes and macrocytes, slight variation in shape, slight polychromatophilia, no normoblasts or stippling.

Four of the eight urine examinations showed the slightest possible trace of albumin, with occasional hyaline casts, twice. The phenolsulphonephthalein excretion was 47 per cent in two hours.

Thirteen stool examinations were made. The bowel movements averaged two per day. All stools were gray, unformed, pasty and shiny. They contained no macroscopic blood, mucus or parasites. Microscopically, numerous sheafs of fatty acid crystals, and, after heating with acetic acid, numerous fat droplets and needle crystals, were evident. No pus or ova were present. The benzidin reaction was persistently negative. The mercuric chlorid test for bile was always strongly positive. The increase in fat and fatty acids gave a striking contrast to the stools of other patients on the same house diet.

Proctoscopic examination showed no apparent atrophy of the mucosa of the rectum.

#### RESULTS OF BLOOD ANALYSES

	Whole Blood, Gm per 100 C c	Plasma, Gm per 100 C c
Lecithin		
Normal, fasting	0.30	0.22
Patient { Before meal	0.24	0.12
{ After meal	0.26	0.12
Cholesterol		
Normal, fasting	0.21	0.22
Patient { Before meal	0.15	0.12
{ After meal	0.15	0.12
Total Fatty Acids		
Normal, fasting	0.36	0.38
Patient { Before meal	0.51	0.29
{ After meal	0.40	0.30

Gastric analysis of the fasting content and specimens withdrawn at forty-minute intervals following an Ewald test meal showed a persistent anacidity and a low total hydrochloride content, never requiring for titration more than 14 cc of tenth normal sodium hydroxid per hundred cubic centimeters. Microscopic examination of the fasting contents showed no food residue, no sarcinae, yeast cells or Oppler-Boas bacilli. The benzidin reaction was negative.

Roentgen-ray studies of the gastro-intestinal tract revealed no abnormalities. The actual emptying time of the stomach was three and one half hours.

The patient raised a moderate amount of mucoid sputum, which on two occasions showed no tubercle bacilli. Both fresh and digested specimens were examined. The Pirquet test was but slightly positive at the end of twenty-four hours. Roentgen-ray examination of the chest showed cloudiness of the superior mediastinum, more marked on the right, and obscuring somewhat the lung field in the region of the right apex. This was suggestive of large mediastinal glands.

The patient's blood sugar was found to be 12 mg per hundred cubic centimeters. The basal metabolic rate was found on two successive occasions to be  $-7$  and  $-8$ . Seventy-two minutes after eating 413 gm of beefsteak, the metabolic rate had risen to  $+15$ . After 147 minutes, it was  $+14$ .

The Wassermann reaction on the blood serum was negative.

A study of the patient's ability to digest fat was attempted. He was given 100 gm of fat in the form of 20 per cent cream and butter. Blood samples were analyzed for lecithin, cholesterol and total fatty acid content both before and five hours after the meal. The results are summarized in the accompanying table.

It will be noted that the lecithin, cholesterol and total fatty acid content of the whole blood was low, likewise, the cholesterol and lecithin content of the plasma was below the normal amount. Of greater significance is the fact that none of the amounts were found to be increased following the ingestion of the meal.

On another day, the duodenal contents were withdrawn on a fasting stomach, and the ability to digest olive oil, boiled and unboiled starch, and casein was studied. In each instance, the control tubes, containing the foregoing substances minus the duodenal ferments, showed no change after eighteen and thirty hours' incubation, whereas, practically complete splitting was accomplished by the patient's duodenal ferments. Quantitative estimations of the pancreatic ferments showed the amylase and trypsin content to be normal, the lipase slightly less than normal.

The fat content of the blood was also studied. One hundred and seventy cubic centimeters of blood was withdrawn and carefully mixed with four volumes of 95 per cent alcohol. Bloor's method for determining the presence of unsaturated fatty acids was employed. The fat took up no iodine, indicating the absence of unsaturated fatty acids.

On a standard Schmidt-Strassburger diet, the fat output in the stools was found to be 19 per cent of the intake, whereas, the normal was considered to be about 5 per cent. Of the fat present in the stools, about 77 per cent was present as fatty acids and soaps. These tests would indicate satisfactory digestion, but incomplete absorption.

Hydrochloric acid was given over a considerable period without appreciable effect.

*Diagnosis*—Because of the blood picture and the pallor, the diagnosis of pernicious anemia was considered, although the blood picture was not entirely characteristic. The degree of prostration, moreover, was out of proportion to the anemia. This latter fact, together with the presence of pigmentation, low blood pressure, anemia and fatty stools, suggested Addison's disease with intestinal tuberculosis.

During the stay in the hospital, the patient's strength improved somewhat, and he was finally discharged on the forty-ninth day with the diagnoses: pernicious anemia? Addison's disease? tuberculosis of the retroperitoneal lymph nodes?

*Course and Readmission*—After leaving the hospital, Feb 6, 1917, the patient had about three bowel movements a day, and was troubled by considerable epigastric fulness and borborygmus. He became progressively weaker, his appetite failed, and he lost so markedly in flesh that, on readmission, April 8, his weight, which on discharge had been 58 kg, had fallen to 43 kg. Physical examination, save for increased wasting, was unchanged. The stools retained their previous characteristics. Examination of the urine was negative on four occasions.

Examination of the blood showed the hemoglobin to be 62 per cent, the red blood cells, 2,568,000, the white blood cells, 3,800 per cubic millimeter. The differential count was: polymorphonuclears, 70 per cent, lymphocytes, 30 per cent. The red cells showed moderate variation in size, slight variation in shape, polychromatophilia, rare stippling and no normoblasts. The temperature, pulse and respiration were normal.

The patient remained in the hospital eleven days before he died. During this time, the temperature ranged between 96.4 and 98.8 F, averaging about 97.6. The pulse varied between 80 and 90, the respirations between 16 and 20. During his stay he complained of no pain or discomfort, and he increased in weight from 43.2 to 44.0 kg. On the day before his death, physical examination revealed the development of a few small red spots about the size

of a dime near the tip of the tongue, which the patient stated had become rather painful. The heart was slow and regular. The lungs were clear save for a few râles at both bases posteriorly. The abdomen was tympanitic throughout, not distended and very slightly tender on pressure. No masses were felt. The liver and spleen were not palpable. Mentally, the patient was clear and alert.

At 3 30, the following morning he was unable to talk, eyes wide open, respirations rapid, pulse weak. At 5 o'clock, the heart was absolutely irregular both in force and rhythm, with an apex rate of 120. Respiration continued to be rapid but regular. The lungs were full of coarse râles. The patient soon lost consciousness, and died at 7 10 a m, evidently from cardiac failure.

*Necropsy Findings*—Necropsy was performed six hours postmortem by Dr E W Goodpasture. It was restricted to the abdomen. On abdominal incision, the complete disappearance of subcutaneous and intra-abdominal fat was evident. There was no excess of fluid. The peritoneal surfaces were smooth and normal. The most striking feature was the enlargement of the mesenteric lymph nodes.

The liver appeared normal. The capsule, which was smooth, was a dark, purplish brown. The weight of the liver was 1,050 gm. The biliary passages were normal. Microscopically, the beam-work of liver cells appeared rather thin, and showed some increase of mononuclear cells in the sinusoids.

The spleen was small, weighing 70 gm. On section, the blood vessels and fibrous tissue trabeculae were very prominent, whereas, the splenic follicles were small.

The esophagus and stomach were normal, except for slight injection of the blood vessels of the gastric mucosa. Beginning at the duodenum and extending to the ileocecal valve, numerous granules were to be seen over the entire surface, appearing as minute elevated grayish dots about 1 mm in diameter, projecting above the surface. In every respect, they gave the appearance of solitary lymph follicles. They were, however, far more numerous than the normal. No Peyer's patches were noted, but, especially in the upper portion of the bowel, from ten to twelve of these small granules were irregularly grouped at intervals. These groups did not closely resemble Peyer's patches. The contents of the small intestine consisted of a small amount of yellowish mucoid material.

Numerous sections of the small intestine were examined microscopically. All showed a thin, loose edematous submucosa with dilated vessels beneath the lymphatics and veins. In places, the edema was more or less circumscribed, forming slightly elevated nodules. The mucous membrane was thin and somewhat atrophic. All the follicles were large, and the villi short, with many lymphoid cells in the interglandular tissue. There was, however, no leukocytic infiltration.

All the mesenteric lymph nodes were considerably enlarged. Grossly, they gave the appearance of hyperplasia, being gray, semitranslucent, and uniform on cut section. The lymphatics, though visible were not prominent. The lymphatic enlargement was confined to the small intestine and to the mesenteric lymph nodes, the glands elsewhere appearing normal. There was no evidence at necropsy of superficial glandular enlargement or of hyperplasia of the lymphatic elements of the spleen. All the mesenteric lymph nodes examined microscopically were in a high degree edematous with dilated sinuses and a prominent reticulum. The peripheral sinuses of the nodes were small. The lymphoid tissue was abundant. Solid masses of lymphoid cells filled the centers corresponding to the follicles. About these, the cells in the reticulum were rather closely packed. There were no dilated lymphatics in the surrounding nodular lymphatic tissue, and no germinal centers were evident.

The large intestine was greatly distended with gas and soft, pasty, sticky fecal material, which, from its pale, gray color, was apparently very fatty. The mucosa of the large bowel was normal, without lymphatic hyperplasia.

The kidneys save for slight congestion and the presence of pin-point yellowish, opaque dots, were normal macroscopically and microscopically.

The bladder, seminal vesicles and prostate were likewise normal

*Pathologic Diagnosis*—Emaciation, hyperplasia of the lymphatics of the small intestine and mesenteric glands, atrophy of the liver and spleen, congestion of the kidney and Meckel's diverticulum were diagnosed

*CASE 2—History*—M R R, a woman, aged 44, unmarried, who had always lived in New England, entered the hospital, Feb 16, 1917, complaining of abscesses of the feet, ulcers of the cornea, and constipation followed by diarrhea

The family history showed that her father had died at 74 of angina, while her mother was still living at 80 There was no family history of cancer, diabetes, tuberculosis or hemophilia Several members of the family were said to have suffered from gout The personal habits were good

The patient had usually enjoyed good health She had had measles twice, chickenpox, whooping cough, a light attack of influenza and occasional sore throats There had been no known exposure to tuberculosis She had sustained no injuries, nor had she undergone any operations The appetite was fair There was habitual constipation Catamenia was established at 15, recurring irregularly every three weeks and lasting three or four days At the age of 24, following a fall into the water, she experienced a cessation of her periods, and there had been no subsequent flow There had been no incidents indicative of nervous derangement

The best weight had been 125 pounds (56.8 kg), the weight, one and a half years previous to admission, was 85 pounds (39.6 kg), and on admission, 71 pounds (32.2 kg)

The present illness dated from two years previous to admission, when the patient noted that the ankles were slightly swollen and that she was losing her customary vigor She was not incapacitated Swelling of the feet and ankles gradually became so pronounced that she consulted her physician, who could find nothing definitely accountable for the edema One year previous to entrance, the swelling diminished, only to recur eight months previous to entry Four months previously, an abscess appeared on the anterior surface of the right ankle, followed by a similar one on the dorsum of the left foot, and, a few weeks later, by a small abscess just below the left knee All of these were incised, but failed to heal satisfactorily One week before admission, the eyes seemed somewhat blurred and watery On examination, a corneal ulcer was found, and ointment and hot compresses were prescribed She had experienced no pain whatsoever The bowels had moved somewhat more freely than usual, following the administration of cathartics by her physician, but the movements were not watery

*Physical Examination*—The patient was a small extremely emaciated, middle-aged woman She was mentally clear The skin was pale, smooth, dry and somewhat inelastic, this inelasticity being due in part to the practical absence of subcutaneous fat The face, with prominent malar eminences and temples and sunken cheeks, presented a cadaverous appearance Just to the mesial side of the center of the right eye was a corneal ulcer the size of a pinhead There was a moderate degree of photophobia and lachrymation No edema of the lower lids was evident The lips were of normal red color, the teeth in excellent condition The tongue, which was clean, smooth and glossy, protruded in the midline, with a moderately coarse tremor The thorax was symmetrical, flat and emaciated in the extreme, with the clavicles extending high above the surrounding tissues The apex impulse could be neither seen nor felt The right cardiac border measured 4.5 cm, the left, 10 cm, from the midsternal line The first sound was distant, feeble, dull and muffled, the second, rather loud and ringing The radial pulses were equal, regular and synchronous The vessel walls were palpable but not sclerosed The systolic blood pressure was 114, the diastolic, 80 The lungs were normal The abdomen was level and symmetrical, but was held so tensely as to make satisfactory palpation impossible The vessels of the abdominal wall were moderately dilated, but not sufficiently so to indicate compensatory circulation The liver, gallbladder, spleen and

kidneys were not palpable. The lymph glands, with the exception of one small, shotty nodule on the left sternocleidomastoid muscle, were not palpable. All the bones seemed essentially normal.

The arms were markedly emaciated, but the nails showed no trophic disturbances. There were no tremors, involuntary athetoid or choreiform movements. The fingers were not clubbed. The radial periosteal, biceps and triceps jerks were active and readily elicited. The skin over the backs of the hands and over both elbows was reddened, thickened and blotchy.

The legs, feet and ankles were moderately edematous, pitting readily on pressure. On the anterior aspect of both external malleoli were two ulcers, 0.5 cm. in diameter, shallow in type, with clean, overhanging edges. A smaller ulcer was to be seen over the left infrapatellar ligament. These ulcers were discharging a slight amount of yellow pus. Both feet were practically the temperature of the room, the coldness extending upward to about two hands' breadth above the ankles. The reflexes were normal. Although on admission the patient's temperature was 97.8 F, during the evening, per rectum, it was no higher than 94.0 F. The pulse was 82, respiration, 20. The patient was seen by an eye consultant on the day following admission. He stated that the corneal ulcer was superficial, and due, probably, to general nutritional disturbance.

*Laboratory Findings*—The urine was acid and clear, with a specific gravity of 1.018. It contained no albumin or sugar. The sediment showed a few leukocytes and occasional epithelial cells. The hemoglobin content of the blood was 75 per cent, the average of four red cell determinations was 3,000,000. Although the color index was +1, the smear showed none of the characteristics of pernicious anemia. The white blood cells numbered 4,000 per cubic millimeter. Two stools were acid, yellow and watery, with much apparent mucus, but no evident blood. The benzidin test was moderately positive. No parasites or ova were evident on microscopic examination.

*Course*—The morning of the second day, the patient, who had been bright, became dull and stuporous, with a pulse rate which had dropped to 44 per minute. Atropin was administered subcutaneously. By early afternoon, she was herself again, sitting up in bed, talking and joking. The heart rate had risen to 65. On the afternoon following the attack, the carbon dioxide in the alveolar air measured 24 mm. of mercury, but no acetone or diacetic acid was found in the urine. The patient was clear mentally, and recalled her condition of the earlier part of the day, she "could not understand why she had been so sleepy."

The third day following admission, she awoke at 5 a. m., and began to talk irrationally. The heart rate was 41, blood pressure, systolic, 86, diastolic, 64. Mouth, axillary, and rectal temperatures taken practically simultaneously showed a continuation of the low temperature of the previous day, namely, 89.0, 89.0, and 90.8 F, respectively. In order to obtain these temperatures, a special clinical thermometer was necessary. During the morning, the patient continued to be irrational. By 11 a. m., the heart rate had gradually risen to 88.

At noon, the patient was found in what appeared to be typical tetany, rigid, with feet very markedly extended and hands flexed, the thumb turned in on the palm, and the fingers tapering to a common point. There were no convulsive movements of the face, save at the onset of the tetanic symptoms, when the nurse noted convulsive twitchings of the left side of the face.

Electrocardiographic tracings showed Lead 1 to be nearly iso-electric, and the rate slow, with definite sinus arrhythmia. The condition of tetany persisted, respiration became much quieter, and ceased at 3.15 a. m.

*Necropsy Findings*—Necropsy was performed eighteen hours postmortem by Dr. S. B. Marlow. On primary incision, the tissues were found to be markedly atrophied, containing no evident fat. The abdominal wall was extremely thin, the rectus abdominus muscles appearing as thin, tense bands.

The abdominal cavity contained 500 c.c. of a milky, white fluid. The entire peritoneum was pale and watery.

On removal of the sternum, the lungs were found moderately collapsed and wholly free from adhesions. The pleurae were everywhere smooth and shiny. The right lung was somewhat firmer than the left. The anterior surface of the right lung was pale and puffed out, the alveoli in these puffy areas being dilated and filled with air, which was easily expressed, leaving the lung collapsed. At the base of the right lung, there was an irregular, depressed scar, which on section was fibrous and tough. In the center, about 1 cm below the surface, was a caseous nodule 5 mm in size. At the apex of the left lung, there was a similar irregular, depressed scar, above which there were grayish yellow dots. Section through the lung at this point showed it to be firmer than normal. Section of the posterior portion of the left lung revealed a deep red, homogeneous surface. It was quite firm and inelastic, containing practically no air. There were, however, no areas of consolidation. Lobules of the lower lobe stood out distinctly, demarcated by milky white lines. The lower lobe of the right lung was similar to that of the left. Sections showed practically all the alveoli filled with red blood cells and fibrin. There was a moderate number of polymorphonuclear leukocytes scattered generally throughout the lung. Some of the alveoli seemed almost filled with these cells.

The heart was unusually small weighing 130 gm. The loosely adherent epicardium had a watery, translucent appearance. No fat was anywhere visible. The vessels stood out prominently. Numerous white streaks were seen in the epicardium, following the larger vessels, evidently lymphatics. The endocardium was everywhere smooth and pink, and heavily streaked with gray. The valves were normal. The papillary muscles were much flattened and atrophied. On section, the myocardium appeared a homogeneous brown. Microscopic examination revealed small muscle cells, the muscle bands being separated by edema. The interstices contained numerous vesicular bodies, and the nuclei of the cells were surrounded by considerable pigment.

The stomach was normally situated, contracted and of a normal external appearance. On section, it was found to contain much mucous material. The mucosa, which was thickened and markedly edematous, was seen microscopically to have undergone considerable postmortem change, with numerous fairly well preserved parietal cells still present. The chief cells were for the most part desquamated and disintegrated, but numerous round and plasma cells were found.

The intestines were light yellow, especially in the upper portion, where numerous yellow patches from 1 to 3 mm in diameter were to be seen scattered diffusely through the wall. Those patches lying opposite the attachment of the mesentery seemed distinctly paler in color. Microscopically, the mucous membrane had undergone considerable postmortem change, with almost complete desquamation of the cells lining the villi. The loose connective tissue in the submucosa just beneath the muscularis contained numerous large mononuclear cells, and multinucleated giant cells containing a finely vacuolated cytoplasm. These cells apparently contained fat. The colon was small, the esophagus normal.

The liver was small, weighing 560 gm. Projecting from the lower edge of the right lobe was a typical Riedel's lobe. Above it, the liver capsule was thickened and fibrous. The liver capsule was firm and somewhat difficult to cut. On section, the surface was a homogeneous grayish brown, with distinct lobules, whose centers were a deeper color than the portal areas. On microscopic examination, the cell columns of one-half the lobule were atrophied, the cells being loaded with fine golden pigment granules. Because of atrophy of the cytoplasm, the nuclei, which were smaller and more deeply staining than the normal, appeared very numerous. The gallbladder was normal and free from adhesions.

The pancreas was a watery yellow, but normal in size and position. The cut surface was granular and yellow, but without any evident connective tissue increase. The pancreatic and acinar cells contained no zymogen, microscopically, but otherwise the pancreas appeared normal.

*Physical Examination*—The patient was extremely emaciated. He lay comfortably in bed, mentally alert and cheerful. His features were sunken, with prominent bony eminences, which gave him a strikingly cadaverous expression. The skin was of normal color, dry, flabby and smooth. It had lost its elasticity, so that when pinched it retained its position for a perceptible interval before spontaneously resuming its former flatness. This property made it doughy to the touch. The lips and mucous membranes were moderately pale. The lungs and cardiovascular system were normal. The systolic blood pressure was 90, the diastolic, 70. The abdomen was slightly rounded, doughy, asymmetrical, with a definite tympanitic prominence to the left of the umbilicus. The scar of the old right rectus incision was evidently the result of healing by primary intention. There were no signs of fluid, and no abnormal masses, spasm or tenderness. Visible peristalsis was definite. No lymphatic enlargement could be demonstrated. Except for marked emaciation, the extremities were negative. Proctoscopic, rectal and ophthalmoscopic examinations were negative. The blood Wassermann reaction was negative.

The patient's temperature ranged from 97 to 99 F, averaging about 97.2 F. The pulse rate averaged about 70 per minute during the first few days, gradually rising toward the end to about 90. The respirations remained at about 20 per minute.

*Laboratory Findings*—All of the fourteen stools examined were light yellow, and contained no parasites or ova, no fatty acid crystals, no gross or occult blood and no mucus. The number of bowel movements ranged from one to three a day, although on three occasions there were as many as five.

The hemoglobin content of the blood was 60 per cent, the red cell count, 2,050,000 per cubic millimeter. The white cells numbered 3,800 on admission. The polymorphonuclear cells were 45 per cent of the total, the lymphocytes, 35 per cent, the large mononuclears (transitionals) 20 per cent. Many macrocytes were seen. Some red blood cells showed marked achromia, others, none. Four normoblasts were found. On three successive occasions during the patient's twenty-five day stay in the hospital before death, the white count varied from 4,000 to 5,400 per cubic millimeter. The hemoglobin (by Sahli's test) averaged 66 per cent and the red blood cells averaged 2,500,000 per cubic millimeter.

The urine was always light yellow, with the slightest possible trace of albumin, but no casts, and only a few white cells. On three occasions, it was acid, on one occasion, alkaline.

Two examinations of phlegm which the patient raised on two different occasions were negative for tubercle bacilli.

On the fifth day in the hospital, gastric analysis, performed after an Ewald test meal, showed the absence of free hydrochloric acid in all specimens, and a total acidity ranging between sixteen and thirty-six. The fasting contents consisted of 20 cc of turbid, mucoid, slightly greenish fluid, containing microscopically many interwoven fungus filaments. There was no gross or occult blood.

Roentgen-ray examination of the chest showed normal diaphragm, heart and aorta. The lung fields were unusually clear. The ribs exhibited no evidence of any abnormality.

A barium sulphate enema showed the outline of the large intestine to be smooth everywhere, with fewer haustra than usual. All parts of the large intestine appeared to be dilated, the capacity being more than 6 quarts (about 6 liters).

Roentgen-ray study of the esophagus, stomach and small bowel revealed no evidence of any pathologic process.

An examination of the duodenal contents showed the proteolytic and amylolytic ferments to be well within normal limits, whereas, the lipolytic

enzyme titer was 0.6 of normal. The method used was that of McClure, Wetmore, and Reynolds.<sup>1</sup>

*Course*—During the first few weeks of the patient's stay in the hospital, the clinical course was uneventful. He did, however, complain of dryness of the tongue, and experienced some difficulty in eating sufficient food to satisfy his caloric requirements. For the first week, he maintained his admission weight of 37 kg, but during the second week, he lost 1 kg.

On the eighteenth day in hospital, the arms felt stiff and numb, on observation, the arms and hands were found in the typical position of tetany. The feet showed no changes, but there was a positive Chvostek sign. The patient complained of no pain. He stated that he had observed exactly similar phenomena one month before entering Peter Bent Brigham Hospital, the condition lasting at that time two hours. By noon, the hands and arms relaxed, and a positive Trousseau sign was readily obtained. The blood carbon dioxide was 14.3 mm of mercury, the blood calcium, 5.3 mg per hundred cubic centimeters, the inorganic phosphate content, 2.6 mg per hundred cubic centimeters. The urine contained no acetone or diacetic acid.

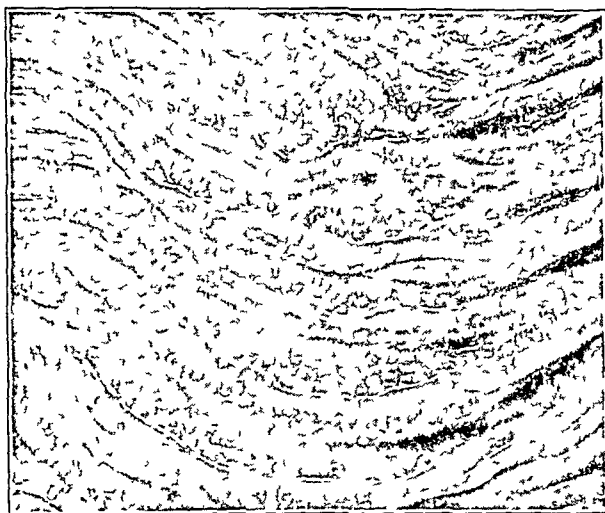


Fig. 2 (Case 3)—Gross appearance of duodenal mucosa, showing numerous granules due to phagocytes in the submucosa containing fat droplets.

The patient did not exhibit any return of the active signs of tetany, although Trousseau's sign could always be elicited. Six days later, on the 24th day, the cathodal closure contraction was obtained with 2 milliamperes, the cathodal opening contraction with 2.5 milliamperes, the anodal closure contraction with 2.25 milliamperes, and the anodal opening contraction with 2.25 milliamperes. The apparatus tested on three normal individuals gave the cathodal closing contraction with 6, 10 and 5 milliamperes, respectively. Despite the use of various diets and medications to combat the steady loss of weight, the patient became gradually more and more emaciated. In view of his precarious condition, on the 24th day of his stay, 500 cc of 10 per cent glucose was given intravenously. It was hoped that, by repeated injections, from one third to one half of the caloric requirements could be introduced. He seemed to take it well, as he made no complaint and his pulse, respiration and temperature were found at half hourly intervals to be normal.

Suddenly, however, about one hour after the injection, he complained of numbness and coldness of the hands and feet, the respiration and pulse mounted

1 McClure, C. W., Wetmore, A. S. and Reynolds, L. New Methods for Estimating Enzymatic Activities of Duodenal Contents of Normal Man. *Arch Int Med* 27:706 (June) 1921.



The spleen, which was small, weighed 30 gm. Its consistency was firm. On section the capsule was markedly thickened, the trabeculae prominent, and the malpighian bodies and blood vessels numerous. There was evidently little pulp tissue remaining.

The mesentery contained numerous milky dilated lymphatics but practically no fat. The lymph nodes were soft, cheesy and enlarged, about the size of a pea.

The kidneys were unusually small and were embedded in a capsule which was loose and edematous. The right kidney weighed 80 gm, the left 60 gm. The capsule stripped with moderate difficulty, leaving a smooth pinkish yellow surface, in which fetal lobulations were pronounced. The cortex measured 5 mm. The striations were regular, and the glomerulae discernible. The pyramids looked normal. Microscopically, the glomerular spaces and kidney tubules were dilated, and filled with pink staining granular vesicular bodies. The picture was that of edema of the kidney.

The pelvic organs were small, fibrous and senile in type, without evident abnormalities. The ovary was microscopically normal.

The parathyroids were carefully dissected out and found to be normal in appearance. Likewise the thyroid and suprarenals presented no apparent abnormalities.

The thoracic duct was carefully explored and found to be free from obstruction anywhere in its course. It contained no fluid.

The bone marrow was a clear translucent yellow, evidently consisting chiefly of fat.

The pathologic diagnoses were brown atrophy of the heart, Riedel's lobe of the liver, hypostatic congestion of the lungs, chylous ascites, emaciation, atrophy of the spleen, bronchopneumonia and fat retention in the intestine.

**CASE 3 History**—F. W. G., married, a clerk, aged 32, entered Peter Bent Brigham Hospital, May 15, 1922, complaining of diarrhea and loss of weight. His family, marital and occupational histories were not significant. His habits were good. He had lived in Boston for about twenty years, after which he had spent one year in the South, East and West, before finally settling in the Middle West. He had not been in the South for about twelve years. He had had measles in early childhood, and scarlet fever at 10. Otherwise, his health had always been excellent. The bowels had always moved once daily, the appetite had always been excellent, and he had never suffered from gas, hematemesis, distress, colic, icterus or abnormal stools previous to the onset of his illness.

The patient considered himself perfectly well until sixteen and a half months previous to admission, when, without evident cause, he developed a painless diarrhea, with from six to eight loose, watery stools daily, without blood or mucus. One year previous to entry roentgenograms were taken of the gastrointestinal tract and the patient was told by his local physician that the diarrhea was due to the appendix, which pressed against the stomach. His diarrhea continued, unaccompanied by any other gastro-intestinal symptoms, he lost 40 pounds (18 kg.) in weight, became worried and finally went to a hospital, asking to have the appendix removed. At operation, eleven months previous to his entry at Peter Bent Brigham Hospital, the appendix and the other abdominal organs were considered normal. He remained in the hospital ten days, and the wound healed by primary intention, but diarrhea persisted, and weakness increased. For the first time, he began to vomit practically everything he ate.

He attempted various forms of dietetic treatment without success, staying in one hospital as long as seven weeks. While there, he developed a single small ulcer on his tongue which persisted for one month and the condition was diagnosed as sprue.

Eight months before admission to Peter Bent Brigham Hospital, he returned home weighing 85 pounds (39.6 kg.), a loss in eight and a half months of 85

pounds, that is, a reduction to one half his original body weight. On returning home, the vomiting ceased, although the diarrhea persisted. The patient ate heartily, and within two months regained 41 pounds (18.6 kg). Five months before entry, he was impelled to consult another physician, who put him on a diet of 3 quarts (about 3 liters) of heated milk and three eggs daily. To this diet, lamb, steak, bread, etc., were gradually added. In three weeks, the number



Fig 1 (Case 3) —Extreme emaciation several days before death

of stools was reduced to about three a day, and these assumed a semisolid character. He continued to lose weight slowly, however, and therefore came to Boston, two weeks previous to admission. His stools averaged three or four daily, becoming slightly looser. His appetite, which, throughout his entire illness had been remarkably good, failed him, and he decided to enter the hospital.

to 40 and 120, respectively, and the face assumed an anxious expression. Believing that the introduction of a hypertonic solution had possibly resulted in an anhydremia, intravenous and subpectoral saline solution to the amount of 1,800 cc was given, without influencing the progress of the patient's condition. Before allowing the saline to flow, a few cubic centimeters of blood was withdrawn. The blood carbon dioxide combining power was found to be 14.3 mm of mercury. Respiration became labored and occasionally hyperpneic. The abdomen was held stiffly, tracheal râles developed, and, at 12:30 a. m., the patient died.

*Necropsy Findings*—Necropsy was performed nine hours postmortem, by Dr. W. S. Quinlan. The primary incision showed an absence of subcutaneous fat. The muscles were pale and atrophic. The peritoneal cavity contained no free fluid, but the intestines were lubricated by a clear, viscous fluid, which on staining showed many endothelial and a few polymorphonuclear leukocytes. There were no adhesions. The mesenteric lymph nodes were markedly enlarged, varying in size from 0.5 to 1.5 cm.

The pleural and pericardial cavities appeared normal. The heart was small, weighing but 180 gm. All the chambers, valves and chordae tendinae were of normal appearance, save that the myocardium was pale and soft, giving the impression of an atrophy with edema. This impression was substantiated microscopically. The spleen weighed 80 gm. It showed moderate wrinkling of the surface, but otherwise appeared normal.

Both grossly and microscopically, the stomach and duodenum were normal. The surface of the jejunum was pink and was everywhere covered by grayish punctate that varied in size from a pinpoint to 1 mm in diameter. These minute elevations simulating distended lacteals on a pinkish background gave a "furred tongue" appearance to the surface. In places, the gray granules were compactly arranged, forming spindle-shaped depressed areas similar to Peyer's patches in appearance, except that they extended along the long axis of the intestine opposite the mesenteric attachment to a point much higher than is ordinarily seen, and were larger in size, measuring 1 by 8 cm. Several sections, examined microscopically, showed dilated vessels and phagocytes in the submucosa filled with fat droplets. Over the lower 100 cm of the jejunum, many roughly circular ulcers were seen, varying in size from 0.5 to 2 cm. The edges of the ulcers were well defined, slightly thickened and beaded with pinpoint grayish elevations. The floor of the ulcers was black, smooth and glistening, giving the appearance of being covered with mucous membrane. None of the ulcers seemed active.

The cecum was distended to about twice its normal size. The mucosa was dull gray, with a few solitary follicles scattered over the slightly thinned wall. The entire surface was coated with a layer of mucous approximately 0.5 cm in thickness. Section through the wall of the intestine showed moderate thickening. Microscopically, the glands were distended with mucus, in places being sufficient marked to have caused actual atrophy of the epithelial cells lining the gland.

The pancreas, liver, gallbladder, suprarenals and genitalia exhibited no abnormalities. The left kidney was normal, the right presented a "V" shaped area of scarring, 1 cm in diameter, evidently an old healed infarct.

The right lung appeared normal, but on section a calcified, nodular mass about 1.5 cm in diameter presented itself, surrounded by gray, fibrous tissue. The left lung was likewise normal save for an area of scarring at the apex which measured 2.5 by 3 cm. Macroscopically and microscopically, the picture was that of healed pulmonary tuberculosis. The larynx, pharynx, tongue and thyroid presented no abnormalities. The brain, dural sinuses, accessory nasal sinuses, middle ears and pituitary were likewise normal.

The mesenteric lymph nodes were definitely enlarged and showed evidence microscopically, of chronic lymph adenitis and hyperplasia.

## COMMENT

These cases, presenting such hazy clinical outlines, evoked considerable interest and speculation. The asthenia, the gastro-intestinal disturbances and the anemia suggested Addison's disease. However, the asthenia was not in any case a primary symptom. Vascular asthenia, as reflected in the blood pressure, did not occur. In only one case was there any disturbance of pigmentation, and in that instance the condition was one of vitiligo rather than chloasma. Finally, the absence of active tuberculosis at necropsy and the presence of apparently normal suprarenal glands justify the exclusion of this possibility.

The anemia, with a high color index, the gastro-intestinal symptoms, the pallor, the gastric anacidity and the asthenia were in accord with the diagnosis of pernicious anemia. The absence of the characteristic blood picture, the marked loss of subcutaneous fat, and the postmortem findings made such a diagnosis untenable.

The presence of prolonged diarrhea suggested a bacillary dysentery and the colitis group of cases. The character of the stools, however, and the postmortem distribution of the lesions in the small intestine rather than in the large bowel, are not in accord with any of these diagnoses.

These cases, particularly the last one, possessed some of the characteristics of sprue. In the last case, the existence at one time of an ulcer of the tongue, the occurrence of an increased number of fatty stools, the anemia, the extreme wasting and the tendency to remission favored this diagnosis.

Other features did not lend themselves to this conception of the disease. 1. The last patient had never visited any endemic center. He had spent one year in the South, where sprue, though very rare, does occur, but this visit had taken place about eleven years previous to the onset of the symptoms, and a latent period of eleven years is difficult to accept.

2. The characteristic tongue lesions were absent. One year previous to the time he came under our observation, the patient had had a small ulcer on the tongue, lasting about one month. During the subsequent course of the disease, when the degree of activity of the condition should have become greatly increased, no lesions appeared. On the contrary, the patient, when questioned, did not complain of the slightest soreness of the tongue or buccal mucosa.

3. The stools were not characteristic. They were not "enormous, fermented, whitish or grayish pultaceous stools, very acid in reaction, and often yeasty in odor, and foamy" <sup>2</sup>

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2 Ashford. Oxford Loose Leaf Medicine 5 631

4 The postmortem findings were not those which have been described as typical of sprue. There was no effacement of the crypts of Lieberkuhn, no deformation of the tubules, no small mucous cysts, no atrophy of the muscle layer of the small intestine, no great thinning of the intestine, and no typical bottle-shaped ulcerations. Moreover, it is of some significance that, whereas the most intense changes in sprue occur in the duodenum and jejunum, the most marked postmortem changes in this case were referable to the ileum. Finally, no organisms, such as have been described by Ashford, were found.

It would seem that a definite clinical and pathologic syndrome with such an intangible etiologic background must have been previously recognized. Nevertheless, search of the literature has uncovered only one analogous case, reported by G. H. Whipple.<sup>3</sup> This case was characterized clinically by a gradual loss of weight and strength, stools consisting chiefly of neutral fat and fatty acids, indefinite abdominal signs, and a peculiar multiple arthritis. Considerable acetone was found in the urine before death. The red blood cells averaged 2,000,000, the hemoglobins 53 per cent. Pathologically, the lesions of interest were found in the intestines and the lymphatics of drainage. The intestinal mucosa showed villi enlarged from deposits of masses of neutral fats and fatty acids in the lymph spaces, and an infiltration of the interglandular tissue by large mononuclear and polynuclear giant cells. The glands showed a similar deposition of fatty substances and a similar inflammatory infiltration.

In the occurrence of fatty stools, great loss of weight and strength, enlarged mesenteric lymph nodes containing fatty substances, tetany (in two), a terminal condition of acidosis (in two), and otherwise essentially normal postmortem findings, the cases here described are similar. On the other hand, none of the cases here described was characterized by arthritis, eosinophilia, fever, purpura or enlarged intestinal villi, as found in Whipple's case. In all essential characteristics these all seem to belong definitely to one disease group.

Many features of the disease excited considerable interest, particularly the appearance of tetany in two of the cases. The low blood calcium is in accord with the findings of Howland and Marriott<sup>4</sup> in children. They found a uniformly low blood calcium, averaging 5 mg per hundred cubic centimeters in tetany, and in no other convulsive disorders. The abatement of the symptoms in the last case after calcium lactate was given by mouth is likewise similar to their experience. The

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3 Whipple, G. H. A Hitherto Undescribed Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic Tissues, *Bull. Johns Hopkins Hosp.* **18** 382 (Sept.) 1907.

4 Howland, J. and Marriott, W. M. *Quart. J. Med.* **11** 289 (July) 1918.

normal phosphate content of the blood in the third case is also in accord with the frequent findings in the tetany of children.<sup>5</sup>

It would seem that the occurrence of tetany in two out of our three cases must be of more than passing significance, in view of the fact that thousands of instances of more severe acidosis constantly occur without producing such symptoms. The exact importance of the low calcium is not clear, for in the acidosis of nephritis the calcium is frequently reduced far more without the production of tetany, although the possibility of the occurrence of the latter is demonstrated by a recent instance in this hospital.

Tetany in adults, although unusual, is by no means rare. In this connection, the reports by Bassett Smith,<sup>6</sup> and by Barach and Murray<sup>7</sup> of two such cases associated with the gastro-intestinal disturbances of sprue, is interesting. The blood calcium in the latter case was 6.5 mg per hundred cubic centimeters, the plasma carbon dioxide 57.6 per cent by volume. The latter authors present the interesting speculation that since the absorption of calcium is effected in combination with fatty acids, and since the absorption of the latter vehicle is faulty in sprue, the low blood calcium is not altogether surprising.

Findlay and Sharpe<sup>8</sup> found a diminished absorption of fat in cases of adult tetany, but absolutely no deficiency in the ability to split fat. These results are similar to the observations made in Case 2.

The acidosis in two of the three cases here reported must have been referable directly to the malnutrition, and not to any nephritic factor, such as has been observed by Marriott and Howland in the acidosis of marasmus in children.<sup>9</sup> The normal nitrogenous constituents of the blood, the normal urinary findings, the normal phenolsulphonephthalein excretion, exclude any serious impairment of renal function.

In view of the marked undernutrition, the low temperature and the necessarily increased body surface in relation to the body weight, the metabolic rate in the third case was higher than has been expected. The marked secondary anemia may have been a stimulating factor, for it has been shown that the metabolic rate in secondary anemia tends to be increased, and it can be shown to fall after transfusion.<sup>10</sup>

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5 Kramer, B., Tisdall, F. F., and Howland, J. Observations on Infantile Tetany, *Am J Dis Child* **22** 431 (Nov.) 1921.

6 Smith, Bassett. Case of Sprue Associated with Tetany, *Lancet* **1** 178 (Feb.) 1919.

7 Barach, A. L., and Murray, H. A., Jr. Tetany in Case of Sprue, *J A M A* **74** 786 (March 20) 1920.

8 Findlay, L., and Sharpe, J. S. Adult Tetany and Methylguanidine: a Metabolic Study, *Quart J Med* **13** 433 (July) 1920.

9 Marriott, W. M., and Howland, J. Phosphate Retention, *Arch Int Med* **18** 708 (Nov.) 1916.

10 Tompkins, E. H., Brittingham, H. H., and Drinker, C. K. Basal Metabolism in Anemia, with Especial Reference to the Effect of Blood Transfusion on the Basal Metabolism in Pernicious Anemia, *Arch Int Med* **23** 441 (April) 1919.

The exact significance of the megacolon in the third case is uncertain. Whether the condition was congenital or merely consequent to the atony of the intestinal musculature, it is impossible to state. The megacolon, the hypermotility, the dryness of the skin, raised the question whether a disturbance of the water metabolism was playing an important rôle. Certain features were not in accord with this conception. The urinary output was always maintained at a satisfactory level. To be sure, in certain diseased states, notably diabetes insipidus, desiccation of the tissues may exist coincidentally with a high urinary output. Pituitary extract in small doses was given to the third patient in an attempt to favor fluid retention in the tissues, but without any influence on the clinical course. If one may assume that the same physiologic factors operate in adults that Marriott has shown exist in children, the presence of an anhydremia in these cases is extremely improbable. In the first place, an anhydremia is accompanied by desiccation of the blood and profound renal damage. Schloss particularly has shown that the degree of desiccation of the blood is proportionate to the degree of renal damage. As previously stated, there was no evidence either during life or postmortem to indicate any serious impairment of renal function.

#### SUMMARY

Three cases are presented, which, because of certain features they share in common, suggest a possible clinical entity. The disease tended to occur in early middle life, with insidious onset, gradual downward progression over a period of one and a half to two years, finally terminating in death. The presenting symptoms were weakness, emaciation, on the average of three soft, semisolid, yellow bowel movements daily, with an excess of fat. Acidosis and tetany were noted in two cases. In the two cases tested, there was an absence of free hydrochloric acid in the gastric contents. Examination of the blood showed a secondary anemia of 2,500,000 to 3,000,000 per cubic millimeter, a color index of approximately 1, but no other indications of primary anemia. All of the special studies and tests were essentially negative.

Pathologically, the significant changes were confined to the intestines and to the mesenteric lymph nodes. In all three necropsies, only incidental changes were found elsewhere. The small intestine showed small granular elevations of the mucosa, usually gray in appearance. Microscopically, these elevations were found to consist of phagocytes containing ingested fat. The phagocytes were large and mononuclear, and contained a foamy reticulated cytoplasm. The mesenteric lymph nodes were noticeably enlarged and hyperplastic, and contained similar phagocytes, with ingested fat.

# CHYLOUS AND PSEUDOCHYLOUS EFFUSIONS

A REPORT OF SEVEN CASES \*

M A BLANKENHORN, M D

CLEVELAND

The purpose of this paper is to describe some unusual observations and discuss the probable cause of milky effusion in each case here recorded. Up to 1910, 242 cases had been reported, as shown in a summary by Wallis and Scholberg<sup>1</sup>. It is probable that many cases have not been published, for there is usually nothing to report save that milky fluids are present, and the milkiness is unexplained. Wallis and Scholberg found 81 cases due to tumors, 46 to infections, of which 33 were ascribed to tuberculosis, and 37 due to affections of the thoracic duct and lymphatics. Seventy-eight remained in a group of general diseases, 22 of which were specified further as nephritis, and 28 as cirrhosis of the liver. These figures are interesting as statistics, but they give milky effusions no diagnostic value, and not until there is definite information in terms of pathologic physiology and anatomy will any particular milky fluid be a helpful diagnostic sign.

Theories abound as to these fluids, as shown by the terminology in reports—chylous, chyloform, adipose and pseudochylous. In the American Medical Dictionary, chylous ascites is defined as “the presence of chyle in the peritoneal cavity due to rupture of a chyloferous vessel.” Chyloform ascites is given as synonymous with chylous. Adipose ascites is “a variety characterized by a milky appearance of the contained fluid due to the presence of cells that have undergone fatty degeneration.” Pseudochylous is “ascites in which the contained fluid resembles chyle in appearance, but does not contain fatty matter.” Of these terms, the only one that we find no fault with is “chylous,” for it implies definite pathology and is well established. The term “adipose ascites” was never founded on fact and has no general use. “Chyloform” and “pseudochylous” are used indiscriminately to designate all milky fluids not definitely chylous, and against them I join the lists, believing that no one has found definitely milky fluids the turbidity of which was not due to the presence of emulsified fat derived from the chyle.

Observers have indeed found unusual substances in milky fluids, but there is as yet no certain demonstration that these unusual substances were the cause of turbidity. In two cases described by Lion,<sup>2</sup>

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\* From the department of medicine of Western Reserve University and Lakeside Hospital.

1 Wallis, R T M, and Scholberg, H A. *Quart J Med*, Oxford **4** 153, 1910-1911.

2 Lion, M G. *Arch de méd exper et d'anat path* **5** 286, 1893.



glucoprotein was found Taylor and Fawcett<sup>3</sup> found an unknown protein, and Joachim found a lecithin-globulin complex, but all of these observers used inadequate methods to exclude fat as the turbid agent, and assumed their respective proteins to be the only possible cause. If we agree, as many do, that fat is the cause of turbidity, there are still many obstacles in the way of a satisfactory classification of these fluids, especially on the basis of their various ingredients. These difficulties are seen in the attempt at classification made by Powell and Hartley.<sup>4</sup> These writers find eighteen points of distinction between chylous and pseudo-chylous, but in all except two instances the difference is a matter of degree, the chylous fluids being more concentrated than the pseudo-chylous. The remaining points deal with the unusual proteins mentioned above—mucinoids and lecithin-globulin. Classification must fail when there are variable factors which cannot be evaluated, such as the presence of inflammation with exudation, transudation of body fluids or alteration in food intake.

This paper was written on the premise that emulsified fat alone is the cause of milkiness, and it aims to point out in each case cited the mechanism whereby fat may appear in an effusion. Such a premise was established by an investigation into the nature of milky effusions, the details of which will be given in another paper. By proving that emulsified fat is the sole cause of milkiness in effusions, we have gone a long way in their classification, and may hope ultimately to make the finding of milky effusions a valuable diagnostic sign.

#### REPORT OF CASES

CASE 1—A white man, aged 40, admitted to hospital, Oct. 12, 1919, having been in four months previously with a diagnosis of mediastinal tumor, had signs of fluid in the right chest, with massive retrosternal dullness and tremendous obstruction of the veins of the neck. Thoracentesis, October 24 removed 1,268 c.c. of milky, slightly hemorrhagic fluid, October 25, 1,060 c.c. of similar fluid, November 11, 1,800 c.c., milky but more hemorrhagic, December 5, 1,000 c.c., milky with less hemorrhage, and Jan. 1, 1920, 1,400 c.c., very creamy with slight hemorrhage. During this time, the patient was receiving roentgen-ray treatment, and he became comfortable enough to be discharged. He was sent to Baltimore for radium treatment. At the present time, April 1922, he shows no signs of tumor, and has had no treatment for one year.

The four specimens obtained were uniform, except in the amount of blood admixture. One specimen, the bloodiest of the four, developed a partial clot. The fluid reaction was alkaline, the specific gravity 1.017. There were 17,760 cells per cubic millimeter, 20 per cent red blood cells and 80 per cent leukocytes. Of the leukocytes, 90 per cent were small lymphocytes. The cells all stained well, and showed no degeneration. Centrifugation threw down a mass of cells, as described above, and small clots. It also brought up a heavy creamy layer, which under the microscope showed coarse and fine spherical bodies, as well as microscopic granules. Prolonged centrifugation brought

<sup>3</sup> Taylor, Frederick, and Fawcett, John. *Tr. Clin. Soc., London* **38** 169 1905.

<sup>4</sup> Powell and Hartley. *Diseases of the Lungs*, 1921.

no further change, nor did standing for a month or filtering through paper. Heat coagulation formed a very heavy clot without the addition of acid, with acid, clotting was complete and the fluid filtered clear. There was no reduction of Benedict's solution. Shaking with ether made very little change in the appearance of the fluid, but the ether on evaporation left a thick, yellow, greasy residue, which smelled like butter. This residue contained no crystals. It stained with sudan III and gave an acrolein reaction when heated.

*Comment*—In this case, it is quite certain that a tumor had developed with subsequent rupture or possibly with actual ulceration of the thoracic duct. The fluid here obtained must have been chyle with an admixture of blood. The formation of the creamy layer on centrifugation or on standing, the large size of the fat droplets and the ease of extracting with ether indicate a coarse emulsion of the fat in generous amounts as the cause of turbidity. Such an emulsion must have been poured directly from chyliferous vessels into the pleural cavity without any process of filtration. Before centrifugation, this fluid was clearly chylous in the accepted term, but the important fact must be noted that when coarse fat particles were removed by centrifugation, the remaining chylous fluid could not be distinguished from the so-called pseudochylous.

CASE 2—A white woman, aged 42, was admitted Feb. 2, 1921, with a diagnosis of metastatic carcinoma of the abdomen and thorax, following a breast amputation two years previously, with later axillary dissection for carcinoma. February 25, a liter of bloody fluid was removed from the left pleural cavity. May 5, the left chest was again aspirated, and 1000 cc of fluid removed. May 6, abdominal paracentesis was performed and 1,800 cc removed, and, June 4, 1,200 cc was removed from the abdomen. June 5, the patient was discharged to her home, where she required numerous tapplings, and died a few months later. There was no necropsy.

In this case, the fluid was alkaline in reaction and had no odor. It was of a brownish-yellow, turbid appearance, and had a specific gravity of 1.020. Centrifugation threw down many cells and brought up a small creamy layer, partly clearing the fluid and greatly diminishing the red-brown color. The cells were largely red cells but there were 260 white cells per cubic millimeter, which stained very well, showing no gross degeneration or vacuolization. Small lymphocytes predominated, but a few large mononuclear cells suggested carcinoma. Only minute spherical bodies could be seen, but there were many ultramicroscopic particles, with rapid brownian movement. Filtering through paper made no change, but filtering through porcelain left a perfectly clear fluid, faintly brownish red. Boiling with weak acetic acid formed a heavy coagulum which, when filtered off, left a clear brown fluid. Salting out with ammonium sulphate,  $\frac{1}{2}$  saturation, gave no appreciable change,  $\frac{1}{2}$  saturation gave a slight precipitate and partial clearing,  $\frac{1}{2}$  saturation gave a heavy precipitate and complete clearing, after which full saturation again threw down a heavy precipitate. No protein was detected after heat coagulation with acid, and the biuret test showed no peptone. There was no glucoprotein, for after heat coagulation there was no reduction of Fehling's solution before or after hydrolysis of the filtrate. Shaking with ether did not clear the fluid, but a small amount of fat was recovered. Prolonged extraction of the dried residue removed 0.129 gm of fat per hundred cubic centimeters, and a trace of lecithin. Filtering through porcelain diminished the total nitrogen from 0.770 to 0.560 gm per hundred cubic centimeters, and diminished the fat from 0.129 to 0.019 gm per hundred cubic centimeters. Amylolytic ferments were not found.

*Comment*—The fluid in this case, after the cells had been removed by centrifugation, conformed to the usual description of pseudochylous fluids, and we may assume that the turbidity was due to fat, for no other substance particularly no lecithin-globulin complex, no nucleoprotein nor mucinoid substance could be found, and with porcelain-filtration there was equal diminution

of turbidity and of fat. Fat here could not be due to degeneration of cells, for the fluid reaccumulated very rapidly, furthermore, no degenerated cells could be found. It is most plausible to assume that, in this patient, in whom extensive metastases were demonstrated in the abdomen and thorax, there was actual obstruction of chyliferous ducts by tumor masses, and the chyle escaped by a process of filtration.

CASE 3—A white woman, aged 29, admitted, August 23, 1915, and discharged, May 7, 1916, had been sick ten days, and the intestinal hemorrhages, leukopenia and a positive Widal reaction indicated that she was suffering from typhoid. Convalescence was very slow, and in the third month, she had a ptosis of the left eyelid and a peripheral neuritis of both legs. The heart at this time was slightly enlarged, and the pulse was frequently as high as 140, although the temperature was normal. In this period, she was very anemic, having but 2,736,000 red cells and a hemoglobin of 60 per cent. A lumbar puncture was made, and a normal cell count was reported. The neuritis was explained as posttyphoid intoxication.

November 29, while still quite anemic and with troublesome peripheral neuritis in the legs, she developed effusion into the abdomen and both sides of the chest, and a general anasarca, although she remained afebrile and had no leukocytosis. At no time during the course of the long convalescence was anything discovered to explain the ascites, much less the milky nature of the fluid. During convalescence, she developed a respiratory infection diagnosed as influenza, an acute streptococcus tonsillitis and a double otitis media, but no evidence was adduced to indicate a generalized infection or tuberculosis, which might have caused peritonitis and pleurisy, thereby obstructing chyliferous vessels. In default of further information, the effusion must be regarded as a sequel of typhoid fever.

Fifty cubic centimeters of abdominal fluid was obtained. This was of a bluish opalescence, had no odor, and was unaffected by centrifugation, settling or long standing. When shaken with ether, it was unchanged in appearance, and the ether contained no fat. It had a specific gravity of 1.008, and an albumin content of 0.2 gm per hundred cubic centimeters. It contained 120 cells per cubic millimeter, largely mononuclears.

Fifty cubic centimeters of thoracic fluid was obtained, identical with the abdominal in appearance and character, excepting that the specific gravity was 1.005 and the albumin content 0.4 gm per hundred cubic centimeters.

*Comment*—The meager data obtained in this case deserve little discussion, but one may say that the general anasarca, seen in the absence of nephritis and cardiac disease, suggests edema due to starvation or anemia. The very low specific gravity, the very low albumin content and probably low fat content suggest that this accumulation of fluid was due to a filtration through membrane made unduly permeable by starvation or prolonged infection. This filtration of a suspension of fat could have come by way of the chyliferous ducts or even from the blood stream. The patient was very anemic, and Bloor<sup>5</sup> has pointed out that in the anemias there is an increase in the lipoids of blood serum. A milky effusion direct from blood capillaries must be considered as a possible cause, and it is regretted that more complete observations were not made as to the nature of the blood serum.

CASE 4—A white woman, aged 33, admitted October 26, 1920, complaining of nephritis and diarrhea, with no previous indisposition except from what was said to be a tonsillitis, had been suffering from the present illness for eleven weeks, it appearing first as a swelling of the feet which progressed in a few days to a general anasarca but with no demonstrable cardiac stasis. The blood pressure was 110, systolic 65, diastolic, but prior to admission, it had been found by her physician to be much elevated. The urine was scanty and of high specific gravity, with much albumin and many casts. Paracentesis was

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5 Bloor, W. R., and MacPherson, D. J. *J. Biol. Chem.* **31**: 79 (July) 1917.

performed, and 700 c c of milky fluid was removed from the left chest. One week later, the right chest was tapped, and 800 c c of milky fluid was removed, after which 3 liters of similar fluid was removed from the abdomen. With the thorax and abdomen quite dry, no disease of the pleura could be defined, and nothing unusual could be discovered by palpation about the abdomen. Six days later, both sides of the chest were tapped, and 800 c c was removed from the left and 500 from the right. The fluid resembled that previously obtained.

The nephritis became rapidly worse, resulting in death within two weeks. Permission for necropsy was not granted.

The abdominal fluid contained no amylolytic ferment, no cholesterol, no lecithin, no mucinoid substance and no glucoprotein. There was no peptone by biuret reaction on a fresh specimen, but when the specimen had stood a month or more, a peptone test was positive. Half saturation with ammonium sulphate and boiling with weak acetic acid cleared the fluid. Centrifugation brought up no creamy layer, and after long standing there was none. Filtering through porcelain reduced the fat from 0.020 to 0.0073 gm per hundred cubic centimeters and gave a clear filtrate. Shaking with ether caused no clearing and the ether contained no fat, but shaking with a mixture of alcohol and ether almost completely cleared the fluid until coagulation of protein occurred. Prolonged extraction of the dried residue with ether yielded about 0.02 gm of fat per

TABLE 1—*Analyses of Fluids in Case 4*

	Fluid from		
	Abdomen	Left Side of Chest	Right Side of Chest
Specific gravity	1.010	1.010	1.010
Total nitrogen *	0.140	0.140	0.143
Sugar	0.075	0.110	0.100
Urea	0.082	0.089	0.084
Chlorids	0.750	0.630	0.625
Fat	0.02	0.020	0.018
Total solids	1.09	1.236	1.188

\* All solids are stated in grams per hundred cubic centimeters.

hundred cubic centimeters, and in this there was no cholesterol or lecithin. The centrifuged residue from all these fluids showed only a few mononuclear cells, which stained well. There was no cell debris.

*Comment*—The fluids obtained from the patient conform absolutely to the pseudochylous type, but other than emulsified fat no substance was found that could cause turbidity, especially no lecithin, no cholesterol, no glucoprotein and no mucin. It might have been doubted whether 0.02 gm of emulsified fat per hundred cubic centimeters is sufficient to cause such turbidity, but proof that it can do so will be presented in another paper. How this emulsified fat escaped into the abdomen and chest must remain a matter of conjecture. There are two sources for such fat—the thoracic duct and its branches, and the blood itself. In nephritis, a condition known as lipemia has been described, in which the blood serum becomes milky, and in this case there may have been a transudation of milky serum without leakage of chyle. Such an explanation is suggested by the uniformity of the fluids from the abdomen and both sides of the thorax. No observation on the fat content or the appearance of the blood was made in this case.

**CASE 5**—A colored man, aged 24, who was transferred from the Cleveland City Hospital by the courtesy of Dr. Scott, with a diagnosis of chronic nephritis with chylous ascites, had had acute nephritis eight months previously in a Southern hospital, and milky fluid had four times been evacuated from

the abdomen Admission to City Hospital was sought because of an exaggeration of the chronic edematous state that had persisted from the onset of the disease

When he was admitted to Lakeside Hospital, the blood pressure was 130, systolic, 90, diastolic, and the urinary output was about a liter a day, with a specific gravity of 1 020, a large amount of albumin and no renal elements He eliminated 45 per cent of phenolsulphonephthalein in two hours, and by the two-hour specific gravity test, he had a maximum variation of 10 points, the highest being 1 025 and the lowest 1 015 He was distinctly anemic, having a red blood count of 1,350,000, and a hemoglobin of 50 per cent The abdomen was tapped on account of extreme distention, three days after admission, and 3,800 c c of milky fluid was evacuated He was placed on a salt-free low-protein diet, and kept in bed, and in spite of the long duration of his illness and its apparent severity, he made a good recovery and was discharged within five weeks very much improved It was impossible to make any addition to the original diagnosis, although tuberculous peritonitis was considered

Since discharge, one year ago, this patient has been under observation in the outpatient clinic, having reported frequently, once to be tapped His blood pressure is sometimes as high as 170, systolic, 120, diastolic, and he has more albumin in the urine than when discharged from the hospital Hyaline and granular casts also have appeared On his last visit, four months after being discharged, he had a phenolsulphonephthalein output of 47 per cent in two hours, and the specific gravity of the night urine was 1 016, and of the morning

TABLE 2—*Analysis of Fluid from Abdomen (Case 5)*

Specific gravity	1 010	Gm per 100 C c
Total nitrogen		0 595
Sugar		0 130
Urea		0 060
Chlorids		0 750
Fat		0 018
Solids		1 575

specimen, 1 009 He remains free from edema and is able to work as a waiter, but continues with marked albuminuria and high blood pressure, due to chronic nephritis

The fluid contained amylolytic ferment as well as dextrose The biuret gave no peptone reaction when the fluid was freshly drawn, but about a month later a positive peptone reaction occurred There was no cholesterol, no lecithin, no mucinoid substance and no glucoprotein Filtering through porcelain cleared the fluid, as did  $\frac{1}{2}$  saturation with ammonium sulphate and boiling with acetic acid Centrifugation brought up a creamy layer, and long standing developed a similar layer Shaking with ether caused no clearing but brought up a faint amount of grease, which stained black with osmic acid Shaking with a mixture of ether and alcohol momentarily cleared the fluid until coagulation of protein occurred Extraction of a dried residue yielded 0 018 gm of fat per hundred cubic centimeters, but extraction of the dried residue of a clear porcelain filtrate yielded only 0 0046 gm of fat per hundred cubic centimeters The fluid was distinctly more turbid than that from Case 4 There were 130 cells per cubic millimeter, 50 per cent being lymphocytes, all stained well and there was no cell debris

*Comment*—This is another definitely pseudochylous fluid, coming from a patient with severe nephritis and anemia, but with no evidence of disease of the thoracic duct or its tributaries As to the mechanism of milky ascites, what was said in the discussion of Case 4 applies here, except that in this instance the oxalated plasma was twice examined and found to be perfectly clear Under the microscope the ascitic fluid showed a few recognizable fat droplets, but although the fat content was the same as in Case 4 unlike the

other this fluid produced a faint creamy layer when centrifugated. From this, it is apparent that turbidity is not an index of fat content, nor is the size of fat particles dependent on total fat content.

CASE 6—A man, aged 32, admitted Nov. 29, 1920, complaining of edema of the legs, shortness of breath and swelling of the abdomen, had been wounded in battle, Sept. 28, 1918, being shot by a machine gun in the thigh. After about six weeks, he was found to have an enlarged heart with signs of aortic regurgitation and arteriovenous aneurysm in the thigh. Before admission to Lakeside Hospital, he was tapped about forty times for large amounts, and according to his own story the fluid at times was perfectly clear and at other times distinctly turbid, but never milky. When he was tapped at Lakeside Hospital, the 11 liters of fluid recovered was amber, and distinctly milky.

He was operated on, and the anastomosis between artery and vein was closed off. Immediately thereafter, the blood pressure, which had been 115 systolic, 65 diastolic, became 145 systolic, 95 diastolic. After a convalescence of four months, during which time he had no reaccumulation of fluid, he was entirely free from disability, and he now is practically well. The change in blood pressure at the time of operation as a result of stopping the leakage from artery into vein can be taken as evidence that blood pressure in the vena cava had been elevated by arterial leakage, and was diminished by the repair. It was seen after operation that pulsations in the jugular vein ceased.

The abdominal fluid was pale yellow and milky, with a fragile clot that settled in the flask. The specific gravity was 1.008.

TABLE 3—*Analysis of Fluid in Case 6*

	Gm per 100 C c
Total nitrogen	0.170
Sugar	0.060
Urea	0.086
Chlorids	0.680
Fat	0.028
Solids	1.028

This fluid contained amylolytic ferment as well as sugar. The biuret on the fresh specimen gave no peptone reaction, but after a time a peptone reaction developed. There was no cholesterol, lecithin, mucinoid substance or glucoprotein. Filtering through porcelain cleared the fluid, and so did heat coagulation with acetic acid and  $\frac{1}{2}$  saturation with ammonium sulphate. Centrifugation brought up a faint creamy layer, as did standing. Shaking with ether caused no clearing, but a small amount of fat was recovered and the dry residue of the whole fluid yielded 0.028 gm of fat per hundred cubic centimeters. Under the microscope, fat droplets were visible. There were 125 cells per cubic millimeter, of which 75 per cent were mononuclear.

*Comment*—This fluid is also of the pseudochylous variety, of low specific gravity, and low protein and fat content. There is adequate reason to suppose there was obstruction to the drainage of chyle into the subclavian vein, for the blood pressure in the cava system was greatly elevated by the leakage of a large volume of blood into the femoral vein at arterial pressure. The theory is offered that, as a consequence of high intravenous pressure, there was back pressure in the lactiferous vessels, with transudation of much diluted and filtered chyle. The blood serum of this patient was perfectly clear, so that it is unlikely that the turbid effusion was from this source.

CASE 7—A white man, who had been in Lakeside Hospital from June 30 to July 30, 1920, was discharged with a diagnosis of parenchymatous nephritis. The urine at that time had a high specific gravity and contained large amounts of albumin and many granular casts, the phenolsulphonaphthalein output was 60 per cent, and the blood pressure was never elevated, being frequently below 100.

He was readmitted, August 21, and continued in the hospital until his death, Oct 8, 1921. The final diagnosis was peritonitis fibrosus, ascites chylosus, chronic parenchymatous nephritis and chronic interstitial hepatitis. During his long stay in hospital, the nephritis made definite progress, so that the urine was even more diminished in volume and contained larger and larger amounts of albumin up to 10 gm per liter. The lowest phenolsulphonephthalein output was 55 per cent. The specific gravity of the urine was always high, with a total volume frequently of no more than 400 c c. He had no fever. The blood nitrogen was never higher than 90 mg per hundred cubic centimeters. For a long time, his appetite was good, and his strength permitted him to walk about the ward. He gradually deteriorated until he was no longer able to be out of bed, and he refused to take food. Toward his latter days, he became very edematous and complained of pain in the upper abdomen. Before death, a roentgen-ray examination with pneumoperitoneum was made, which made him very uncomfortable. A diagnosis of chronic adhesive peritonitis with cirrhosis of the liver was made from the plates.

During the second admission, the abdomen was tapped thirty-six times at intervals varying from three to fourteen days, the average being eleven days. The length of time was dependent on the fluid intake and the physical activity of the patient. Rest in bed and restricted intake prolonged the intervals. He had no medication except an occasional cathartic, sedatives when he complained of sleeplessness, and a short course of antisyphilitic treatment with mercury.

TABLE 4—*Analyses of Specimens in Case 7*

	Greatest	Least
Specific gravity	1.012	1.006
Total nitrogen (gm per 100 c c)	0.490	0.140
Sugar (gm per 100 c c)	0.150	0.060
Urea (gm per 100 c c)	0.100	0.060
Chlorids (gm per 100 c c)	0.750	0.200
Fat (gm per 100 c c)	0.201	0.090
Total solids (gm per 100 c c)	2.9	1.8

and potassium iodid, which had to be stopped on account of increasing albuminuria. The blood Wassermann reaction had been negative.

On one occasion, by feeding a diet rich in butter and cream, the fat content of the fluid was increased from 0.128 gm to 0.201 gm per hundred cubic centimeters, following which it dropped below its former level. As the patient refused the diet, the experiment could not be repeated.

Blood fat, estimated at various times on whole blood, was from 123 to 135 mg per hundred cubic centimeters. At no time was the serum or oxalated plasma abnormally turbid.

Chemical analysis was made of many of the thirty-six specimens, the extreme results of which are given in Table 4. The average of all analyses is approximately the average of these extremes.

These specimens all contained amylolytic ferments when tested, and sugar was never absent. The biuret test on freshly drawn specimens was negative, but after they stood a month or more it was uniformly positive for peptone. In the ether extract, traces of cholesterol and lecithin were occasionally present, but not necessarily at the same time. In one specimen, there was a substance—probably glucoprotein—which was precipitated by alcohol after all heat-coagulated protein had been removed, and which after hydrolysis with hydrochloric acid reduced Fehling's solution. Its presence could be easily demonstrated in one specimen, but never in any previous or subsequent tappings.

Filtering removed on one occasion 93 per cent of fat and 20 per cent of protein, on another occasion, 90 per cent of fat and 9 per cent of protein. Heat-coagulation with weak acetic acid cleared these fluids, as did  $\frac{1}{2}$  saturation with ammonium sulphate. Centrifugation or long standing always brought

up a small creamy layer. Except for this creamy layer and a faint white sedimentation, some of the specimens remained unchanged after more than eighteen months at room temperature in loosely stoppered flasks. Shaking with ether, if prolonged an hour or more in a machine, developed a gelatinous gummy mass, which was difficult to separate from the extracting ether. This mass was always present unless the fluids became acid from putrefaction or by direct addition of acid. Such extraction with ether seldom removed more than 0.030 mg of fat per hundred cubic centimeters, and did not materially clear the fluid. Extraction of the dried residue prolonged for from forty to sixty hours in a Soxhlet apparatus removed all extractable fat, including occasional traces of lecithin and cholesterol. Shaking with a mixture of ether and alcohol cleared all turbidity until coagulation of protein occurred. In fresh specimens the microscope revealed from 120 to 300 cells per cubic millimeter, largely small, readily stainable lymphocytes. Small oil droplets were seen and many ultramicroscopic bodies.

This man died, and necropsy was performed two hours after death. Following is an abstract of the report made by the pathologist, Dr B. S. Kline.

Except for edema of the lower extremities the body showed nothing externally. On opening the abdomen, the parietal peritoneum was found everywhere to be strikingly thickened, being covered with a pearly white membrane, a millimeter in thickness. In places, injected vessels were visible on the surface. Two and one half liters of milky fluid were evacuated. A portion of the transverse colon and stomach were walled off from the peritoneal cavity by a membrane similar to and continuous with the parietal peritoneum, and a similar membrane extended from the right lobe of the liver to the abdominal wall.

On opening the thorax, the right pleural cavity contained 50 c.c. of slightly turbid, yellowish fluid. The left contained 1½ liters of fluid similar to that in the abdomen. There was a similar pearly white membrane over the visceral and parietal pleurae on the left side but in places it was diffusely injected. The pericardial chamber contained its normal amount of fluid. The liver weighed 1,050 gm. It was increased in consistency, and on section portions of the thickened capsule could be seen penetrating the substance of the liver. The vena cava and large branches, as well as the thoracic duct, which was dissected throughout, showed no abnormality.

Histologic examination of the kidneys showed the usual picture of chronic parenchymatous nephritis, with much fatty degeneration but no fat infiltration.

Section of the small intestine showed an unusual gross appearance. The striking thing was the marked thickening of the serosa. The portion toward the muscle was composed of loose areolar tissue, the cells separated by a considerable amount of amorphous pink-stained material. Scattered throughout, there were fairly numerous wandering cells, the majority mononuclear, many of these polyblasts or endotheliocytes. Numerous eosinophils were also present. The outer coats were composed of layers of fibroblasts and newly formed blood vessels, with cells separated by loose, amorphous, pink-stained material. In some areas, there were small mononuclear round cells, and the outermost portion of the wall was partly composed of a thin layer of fibrin, invaded by fibroblasts, or entirely replaced by them. In places, in the depth of the granulation tissue, there were amorphous pink-stained masses suggesting fibrin. In the granulation tissue, no lymphatics were observed, and those in the muscular layer and mucosa were not unduly conspicuous. The impression was gained that the process consisted of repeated depositions and organizations of fibrinous exudate.

Section of the liver and spleen showed this same change within the serosa, as well as atrophy of the liver tissue, but no increase of stroma within the liver lobules.

Section of the parietal pleura showed a thick layer of granulation tissue made up of fibroblasts, sprouting capillaries with prominent endothelium and



wandering cells (small mononuclears, plasma cells and endotheliocytes in about equal numbers) This section gave the impression that the process was a low-grade inflammation, with deposition of fibrinous exudate followed by organization

Section of the mesenteric lymph gland showed the sinuses filled with large endotheliocytes and a considerable amount of amorphous, pink-stained material In areas there were numerous eosinophils and an increase in the stroma of the gland, especially about the blood vessels

The complete pathologic diagnosis was old tuberculous bronchial and mesenteric lymph nodes, encapsulated tubercles in the left upper lobes, chronic diffuse peritonitis with chylous ascites, chronic diffuse pleurisy with chylous effusion, capsular cirrhosis of the liver, beginning involution of the pancreas, chronic parenchymatous nephritis, atrophy and replacement fibrosis of the testes, complete inguinal hernia, right, old fracture of the left tibia Probable cause of death was chronic peritonitis with chylous ascites, chronic pleurisy left with effusion

*Comment*—This fluid from its chemical and physical nature must be classed as pseudochylous Furthermore, although the thoracic duct and its coarser branches, as well as the vena cava superior, were demonstrated free from obstruction, the milky appearance can be shown to have been due to emulsified fat Evidence to this effect is contained within this report, but the major proof will be presented in another paper Presumptive evidence is seen in the fact that the fat content of this fluid was increased by fat feeding—the so-called Strauss<sup>6</sup> sign—which points both to fat as the cause of milkiness and to absorbed fat as the source Fat was present in the form of emulsion, the separate particles of which varied from microscopic globules to ultramicroscopic particles that would pass an ultrafilter

How emulsified fat might occur in this case is not clearly demonstrated by necropsy, but adequate cause is at hand in the extensive fibrosis of intestines and mesentery A second possibility deserving discussion is the formation of fat by degeneration of fixed or exuded cells The extreme rapidity with which the fluids formed in this case—11 liters in three days—speaks convincingly against this explanation Furthermore, no such degenerated cells could be found free in the fluid or in the walls of the cavity generating the fluid Further still, fat formed by degeneration of cells and tissues is disposed in coarse emulsions, often in coarse globules

A third possibility is that a lipemic serum could have transuded from blood capillaries This theory is incapable of being proved or disproved In this instance, the observed serum was never of the same appearance as the fluids in question One argument in favor of this origin is the surprisingly close correspondence between the amounts of blood fat and effusion fat, but against this is the wide disparity in the amounts of serum protein and effusion protein for it is difficult to imagine a filter allowing all the fat to pass but withholding nine-tenths of the protein The very low fat and protein contents are more in harmony with the first theory, that filtration from lactiferous vessels was the mechanism of producing this milky effusion The extensive fibrosis of the intestine and mesentery was quite sufficient to produce stasis at the very origin in chyliferous vessels of small dimensions

In the chemical examination of the fluids described in connection with these cases, sugar was estimated by the Lewis-Benedict method, urea by urease and aeration, chlorids by the method of McLean, Van Slyke and Donley, cholesterol by that of Bloor, followed by the Liebermann-Burchard test, lecithin by acetone precipitation, and phosphorus by the molybdate test Fat extractions were made with

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6 Strauss, M I Arch de physiol norm et path 18 367, 1886

petroleum ether, but on account of the difficulty in obtaining petroleum ether with absolutely no nonvolatile residue, sulphuric ether was used when minute amounts of fat were dealt with

Most of the routine procedures were carried out by Miss Ruth Trump, chemical technician in the medical research laboratory of Lakeside Hospital

#### SUMMARY AND CONCLUSIONS

Seven cases are recorded, in all of which milky fluids were found. In one case, in which the patient had a tumor of the mediastinum, the fluid contained large amounts of fat in coarse and fine emulsion. This fluid can well be called chylous. In the remaining six cases, in all of which the patients were known to have lesions capable of effusion from chyliferous or blood vessels, the fluids contained smaller amounts of fat, in very fine emulsion, these fluids might be classed as pseudo-chylous, but the only difference between them and the first fluid is that they lacked large fat particles.

The terms "pseudo-chylous" and "chyliform" are descriptive, and imply much that is not true and had better be discarded.

The term "chylous" is accurate and general enough to designate all milky effusions save those that can be shown to originate from lipemic blood.

# THE CAUSES OF TURBIDITY IN MILKY ASCITIC FLUIDS \*

M A BLANKENHORN, M D

CLEVELAND

In a companion paper, in which I reported seven cases of milky effusion and described the so-called pseudochylous fluid from each, it was pointed out that there was disagreement as to the cause of the turbidity of such fluids, and as a consequence much confusion among the descriptive terms applied. Some writers hold that emulsified fat is the cause, others, finding very little fat, are unwilling to ascribe turbidity to amounts so insignificant, and still others, finding no fat, ascribe turbidity to an unknown protein or some uncommon substance, such as glucoprotein, mucinoids, or a lecithin-globulin complex. The present work was undertaken with the hope of throwing further light on the subject by investigation into the nature of the turbidity in five of seven fluids described in the previous paper. The results were clear-cut. Emulsified fat was proved in all five cases to be the cause of turbidity.

This finding is in disagreement with that of observers who have found emulsified fat in these fluids but in amounts so small that they considered it inadequate for turbidity. How much fat is necessary for turbidity is a matter often discussed, but the fineness of its division is seldom considered. This investigation deals critically with that point, but credit for priority must be given to Gandin,<sup>1</sup> who made a similar investigation and came to the conclusion that small amounts of fat cause turbidity. The conclusions of this paper are discordant also with those of investigators who find no fat, and it will be shown that their methods do not rule out the presence of fat. Our conclusions are further in disagreement with those ascribing turbidity to proteins, because on removing proteins, principally globulin, turbidity was dispelled, and it will be shown here that the methods used to remove proteins also remove suspended fat. It is therefore fallacious to ascribe turbidity to protein on that evidence.

In this investigation, emulsified fat was found in every specimen. Of the other substances supposed to cause turbidity, the only one found in any notable amounts was glucoprotein, which was present in the twenty-sixth specimen from Case 7, but in no other. Small amounts of lecithin and cholesterol were found, but nothing resembling mucin.

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\* From the department of medicine of Western Reserve University and Lakeside Hospital.

<sup>1</sup> Gandin, S. *Ergebnisse der innern Medizin und Kinderheilkunde*, Berlin, 22 227, 1913.

In order to determine the cause of turbidity, the following plan was followed

- A Microscopic examination
- B Separation of the turbid substance by
  - 1 Filtration
  - 2 Sedimentation
  - 3 Heat coagulation
  - 4 Salting out
  - 5 Mutual precipitation
  - 6 Extraction
  - 7 Freezing
  - 8 Peptization
  - 9 Electrolysis
  - 10 Dialysis
- C Synthesis of turbid fluids by
  - 1 Operation on the thoracic duct of dogs
  - 2 Homogenization of oil, water, protein and salt mixtures
  - 3 Homogenization of oil-water mixtures

Of these various lines of approach, synthesis alone was entirely successful and decisive. Separation by peptization, electrolysis, extraction, freezing or filtration was successful and corroborative in about the order given. Separation by salting out, mutual precipitation, sedimentation and heat coagulation was successful, but the results were open to contradictory interpretations, though in the main reconcilable throughout. Microscopic examination was merely corroborative, and dialysis was unsuccessful.

#### FILTRATION

Filtration was first tried. It was hoped by this means to isolate the substance causing turbidity, and thereby allow identification by chemical examination. Filtering through paper removed nothing, and Mandler filters accumulated no collectable filtrate. When very fine Mandler filters were used, a distinct clearing was noted, but no diatomaceous filter produced complete clearing. This was determined by reading print through tubes of equal diameter and comparing the clearness of the view through the filtered with that through the unfiltered. When coarse Mandler filters were used, there was less clearing.

A Pasteur-Chamberland filter cleared the fluid completely, leaving a straw-colored, limpid filtrate, but the process was always slow and difficult, frequently impossible even with a pressure of 70 pounds, after a certain volume had passed. Several candles, after repeated use and clearing with alkali, became more permeable, thus allowing a filtrate to come through rapidly, but with definite milkiness.

Before filtration, these fluids contained from 19 to 200 mg of extractable fat per hundred cubic centimeters. The filtrates when clear contained from 5 to 19 mg of extractable fat per hundred cubic

centimeters The unfilterable residue was collected with much difficulty and uncertainty as to amount, but by reversing the direction of flow, a small amount could sometimes be washed back This contained fat and protein in variable amounts and varying proportion, in general, the longer the filtration, the greater the relative amount of protein It was apparent at once that the residue could not be taken as the isolated and uncontaminated milky substance, for the longer filtration went on, the less permeable became the filter, until ultimately not even water passed through A certain amount of protein could be further removed from the residue on the filter by washing through with large volumes of saline followed by water, but prolonged washing never produced a residue free from protein On the other hand, long washing compressed the mass into a greasy scum, which was removed from the filter with much difficulty

When filtrates were perfectly limpid, the average of five filtrations withheld 94.3 per cent of all fat and 18 per cent of all protein When filtrates were more turbid, more fat was present Graduated filtration, going on to so-called ultrafiltration, removed more and more fat, and at the same time the filtrates became less and less milky, but always an extremely small amount of fat continued to go through In one instance, 19 mg per hundred cubic centimeters passed the filter, and the filtrate appeared clear This at first sight seems inconsistent, for two of the milky fluids, Nos IV and V of our previous report, contained just that amount But it must be recognized that fat in particles smaller than the wave length of light gives no milkiness, and further that clearness is a relative condition liable to be misjudged by ordinary observation

Filtering through fresh frog skin with a method devised by Sollmann partly cleared the fluid, giving a milky filtrate and very cloudy residue Twenty-five cubic centimeters of a fluid containing 20 mg of fat and no protein was filtered at about 30 cm of water pressure In the 5 cc of residue, there was 11 mg of fat and in the 20 cc of filtrate there was 9 mg, so that 45 per cent had passed through A similar membrane employed in the filtering of dilute ox serum at the same pressure allowed 66 per cent of protein to pass These results by Sollmann's method show that (1) finely suspended fat can pass a vital membrane, (2) protein passes better than fat, and the two substances can be partly separated, and (3) turbidity of these mixtures diminishes with fat content rather than with protein content

By filtering pseudochylous fluids, the turbid substance can be removed from the suspending medium, but it is not isolated in pure form Protein and fat are found both in the residue and in the filtrate, but fat is concentrated in the residue and turbidity is confined to it Filtering through vital membranes allows more fat and a turbid filtrate

to pass We can therefore conclude that fat particles are present in variable size, some are small enough to pass a porcelain filter and cause no turbidity, but mostly they are too large to pass, and do cause turbidity

#### MICROSCOPIC EXAMINATION

Microscopic examination was undertaken to identify the turbid substance *in situ* When the highest power oil immersion was used, the whole fluid was uniformly opaque, the field being composed of minute points with rapid brownian movement, with a few definitely spherical bodies A filtrate when clear showed no particles, but the residue showed clumped-up bodies too small to be defined, among which were numerous globules After long sedimentation or centrifuging, a thin filmy cream came up, composed principally of spherical forms, and the middle portion thus centrifuged showed no spherical forms, but granules with brownian movement There was no sediment until the fluids had stood several months and then very little in a liter flask, and the body of the fluid was in no degree cleared

From this it is apparent that these fluids contain particles in suspension as a dispersoid, some large enough to be recognized as definitely spherical, others too small to be defined The spherical forms were never larger than one-fourth the diameter of a red cell, most of them were smaller, but no one size seemed to predominate When filtration had cleared the fluid of milkiness, these suspended particles had disappeared

#### SEDIMENTATION

Sedimentation was expected to isolate or at least concentrate the turbid substance After standing a few days, the surface of these fluids all showed a more or less delicate film of bluish white, a creamy pellicle Vigorous centrifuging—several hours at 2,300 per minute—produced the same effect This pellicle could be made to disappear into the underlying fluid by very little shaking When removed by a pipet, it could be freely suspended in distilled water or saline and again centrifuged out, and the natural pellicle formed by long standing behaved in the same manner After the entire pellicle was removed, no amount of centrifuging could form another, not even after the addition of cane sugar sufficient to raise the specific gravity to 1.060 or salt to bring it to 1.080 The sediment seen after these fluids had been standing six months or more could be resuspended by shaking, and except for that part which was definitely flocculent or threadlike, it was a long time resettling

From the bottom of a 2-liter flask that had stood sixteen months uncontaminated, a small amount of sediment was removed by pipetting

This sediment was largely composed of needle crystals, single or in rosette clusters. The clusters were about 15 microns in diameter, and the crystals were about 7 microns long. This residue was insoluble in dilute alkali, acid, alcohol or ether. It was then tested for tyrosin and ammonium urate, and neither was found, but small amounts of an ether soluble substance was extracted, which gave reactions for cholesterol and lecithin.

From sedimentation of these fluids, it is shown that spherical bodies of appreciable size rise to the top after long centrifuging, making the top more turbid, but the bulk of dispersoid is composed of particles so small that physical forces, probably surface tension and surface charge, overcome sedimentation.

#### HEAT COAGULATION

Heat coagulation was employed to remove the greater part of the protein, leaving other substances in solution or suspension. Boiling produced no immediate change except in No. IV, which had an uncommonly large amount of protein, but on standing a few hours all showed more or less sediment and no clearing. Heating and acidulation formed a flocculent precipitate, which if undisturbed settled out, part going up and part becoming sediment, leaving a clear liquid. This coagulum from heating and acidulation when dried and extracted contained all the fat originally contained in the fluid. From this procedure, it is seen that heat coagulation of protein removes fat as well as protein, just as egg clears coffee. The clear filtrate from filtration through porcelain when heated produced an opalescence resembling that of the unfiltered fluid, but this milky fluid on standing under sterile conditions formed a generous sediment and eventually cleared again.

#### SALTING OUT

Salting out was employed to remove and isolate proteins. Diluting with 19 volumes of water at  $p_H$  7 formed, after twenty-four hours, a faintly granular precipitate, which required several days for complete sedimentation. After sedimentation the fluid was still quite turbid, although the milkiness was much dissipated by the original diluting process. The collected precipitate when redissolved by adding crystals of salt did not make a perfectly clear solution.

Ammonium sulphate solution saturated at 32 C was used, so that  $\frac{1}{5}$ ,  $\frac{1}{4}$ ,  $\frac{1}{3}$  and  $\frac{1}{2}$  saturation could be obtained. With  $\frac{1}{5}$  saturation there was, after twelve hours' standing at incubator temperature, a very faint precipitate, so faint that it was collected with great difficulty and was frequently lost. When this precipitate was redissolved in saline it made a faintly milky solution. With  $\frac{1}{4}$  saturation, a

considerable amount of precipitate formed, with a slight clearing effect, and when filtered and washed with  $\frac{1}{4}$  ammonium sulphate and redissolved, it gave a distinctly milky solution. One-third saturation gave even more precipitation and more clearing of the fluid, and the precipitate on redissolving was very milky. At  $\frac{1}{2}$  saturation, more precipitate formed, and usually a perfectly clear filtrate resulted. This precipitate when redissolved gave a milky fluid of the same appearance as the original untreated fluid. Saturation with ammonium sulphate crystals completely cleared the fluid and removed all proteins.

When dried and extracted in a Soxhlet extractor, the various fractions brought down by different degrees of saturation all contained extractable fat and all gave turbid solutions. Fractional salting out was done again in the same steps, but each portion was removed as it was thrown down, making way for each succeeding step. In this manner five fractions were collected, all containing protein and all containing fat. No fraction greatly exceeded any other in fat content, but the last one—presumably serum albumin—alone contained amounts too small to be measured. The fraction at  $\frac{1}{2}$  saturation was more bulky than any other, and probably contained more protein. These fractions were separated by centrifuging, and quantitative determinations of protein were not attempted on account of the difficulties involved in washing free from ammonium sulphate. It was apparent that fat was precipitated by any degree of saturation that precipitates globulin, and that  $\frac{1}{2}$  saturation precipitates all fat. There was apparently a zone of saturation,  $\frac{1}{3}$  to  $\frac{1}{2}$ , that produced a precipitate heavier than others. Whenever globulin came down, fat came down in direct proportion, but when the clear filtrate after  $\frac{1}{2}$  saturation was dried and extracted, at most only a few milligrams of fat per hundred cubic centimeters were found. In each specimen, the precipitate obtained with  $\frac{1}{2}$  saturation when dried and extracted contained practically the same amount as could be obtained by extracting the dried residue of the whole fluid. A clear filtrate from porcelain filters when treated by  $\frac{1}{5}$ ,  $\frac{1}{4}$ ,  $\frac{1}{3}$  and  $\frac{1}{2}$  to full saturation gave a precipitate with each fraction roughly equivalent to those of the unfiltered.

By every method tried—diluting and salting out with sodium sulphate or ammonium sulphate—whenever a precipitate of protein was formed fat also was precipitated. No globulin body free from fat could be obtained except that salted out from a fluid previously filtered clear. This might be thought to indicate a combination, chemical or otherwise, between fat and protein, but it will be shown later that all the salting out methods used to precipitate protein will likewise precipitate fat from a suspension in pure water. Salting out, like filtration, removes the turbid substance but does not isolate it.



## MUTUAL PRECIPITATION

Mutual precipitation by various substances was employed to isolate the turbid body. When kaolin was added and the fluid well shaken and allowed to settle, no clearing was noted, nor was there any on adding animal charcoal, calcium hydroxid solution or hydrated silicate of aluminum. Ferric hydroxid produced a precipitate with the first drop added, and further addition precipitated all suspended matter, leaving a clear supernatant fluid. This clear fluid when dried and extracted contained no fat. Arsenous sulphid gave no precipitation. When alkalis were added, no change was noted in the milkiness and no precipitate was formed, the fluids being always alkaline when freshly obtained and more alkaline as they became older, even though uncontaminated by bacterial growth. When acids were added, no change was seen until the neutral point was passed and a  $p_H$  of 5 + was reached, when a flocculent precipitate formed and settled to the bottom. Stronger acid produced a heavy precipitate, amounting to a coagulum, thus clearing the fluid. The filtrate obtained by filtering through porcelain, when treated with acid to the same degree of acidity as determined by indicators placed directly in the fluid, formed no precipitate. When more acid was added, a precipitate formed, more acid being required to form the first precipitate in the filtered than in the unfiltered.

By mutual precipitation of colloids, it is shown that a colloid of positive charge, such as ferric hydroxid, will precipitate all protein and all fat, and that negatively charged colloids, such as arsenious sulphid, kaolin or charcoal, produce no change. It is also seen that, when fat is present in the system, acidulation beyond the iso-electric point of albumin and globulin causes a flocculent precipitation, but with the fat removed, acidulation beyond that point causes no precipitate or very little after considerable time. Suspended fat is known to carry a negative charge, as explained later in the section on electrolysis, and globulin and albumin carry negative charges when in an alkaline medium. In an acid medium, fat suspensions are still negative, but protein becomes positive, we then have oppositely charged particles and mutual precipitation.

It was impossible to separate the turbid substance from other colloids in suspension by any method tried, but whenever fat was precipitated, clearing resulted. Likewise, whenever clearing was obtained, fat had been precipitated.

## EXTRACTION

Extraction was employed to isolate suspended fat. Shaking with ether or petroleum ether in a separatory funnel produced no clearing, and no matter how long the shaking lasted, it extracted very little fat.

Addition of acids or of alkalis produced no additional clearing, but more fat was extracted when sufficient acid was added to produce a coagulum. Never more than 30 mg of fat per hundred cubic centimeters could be extracted by such methods, and this amount was unusual, the average being about 10 per cent of all extractable fat. Removal of this fat had little clearing effect on the remaining fluid, on the contrary, if shaking was much prolonged and ether kept in contact with the fluid for several days, a flocculent coagulum formed, causing more milkiness than before. Petroleum ether had less coagulating effect than had sulphuric ether, but there was no clearing. Shaking with kerosene did not produce clearing, even when kerosene was allowed to run through 300 c c of the fluid in a serpentine extractor, at the rate of 8 liters every twenty-four hours for five weeks, no clearing could be noted.

When the fluids were vigorously shaken with ether, this became emulsified into the water of the fluid, forming a stiff semitransparent gummy mass, which prevented further agitation of the mixture and probably interfered with fat extraction. After long standing, this mixture would settle into three layers, a watery layer below, clear ether on top, and a gummy, almost transparent layer between. The watery layer was less milky than the original fluid and so was the middle layer, but when the ether was evaporated, the fluid promptly returned to its original milkiness and the gummy layer disappeared. The slight clearing effect was a result of the emulsifying of ether into a watery protein solution and not due to any fat solvent action.

By evaporating the entire fluid to dryness and powdering the residue, a constant amount of fat could be extracted in a Soxhlet apparatus. Extracting the dried precipitate from acidulation, heat coagulation or  $\frac{1}{2}$  saturation constantly yielded similar results. Continued extraction for seventy-two hours usually removed all extractable fat and left a dry, fine impalpable powder. The figures for fat content given in the previous paper were from the dried residue extracted seventy-two hours with sulphuric ether. This fat when extracted was found to consist largely of neutral fat and fatty acid, with traces of cholesterol and lecithin.

The powder found remaining in the extraction thimbles was not soluble in water, saline dilute acids or alkalis. When triturated with water, a turbid mixture resulted, which rapidly sedimented out. Stronger alkalis put this powder partly into a solution, from which various protein reactions could be elicited. It was hoped that a soluble residue of protein would remain after complete extraction but the process of drying and extracting rendered most of the protein insoluble in anything but strong acids or alkalis. Proteolytic enzymes, as found in commercial pancreatin, digested this residue, so as to form a moderately clear solution.

The filtrate from porcelain filtration when shaken with ether formed a heavy gelatinous mass similar to that of the whole fluid and prolonged exposure to ether removed no fat but left considerable coagulum in the otherwise clear filtrate, so that the fluid deprived of its turbidity and shaken with ether behaves in no way differently from the original. When shaken with a mixture of equal parts ether and alcohol, three of these fluids could be completely cleared (the two others were not tried), but this procedure had to be carried out with speed and care. As an ether-alcohol mixture, unlike ether alone, was freely miscible with watery ascitic fluid, it was a better extraction fluid, but employment of an excess of alcohol or prolonged exposure to dilute alcohol coagulated protein and obscured whatever clearing effect solution of fat might bring about.

This clearing was best done in test tubes with from 5 to 7 cc of the fluid to be cleared. An ether and alcohol mixture was added, 1 cc at a time, and vigorously shaken to accomplish mixing in the shortest time possible. Very quickly another cubic centimeter of the solvent was added and the tube quickly shaken. When approximately an equal volume of solvent has been added, the mixture suddenly clears and remains clear for a few minutes. It is never brilliantly clear, for small air bubbles are included, but before the protein coagulating effect of the alcohol begins there is a space of from a few seconds to a minute or two in which the solution of suspended fat is accomplished. When an excess of alcohol is added, milkiness returns and remains. If alcohol alone be added just short of the point where it will coagulate protein and then an excess of ether, a similar clearing results.

That fat solution is accomplished by this process was proved by adding ether and alcohol in excess, thus coagulating all protein. After this, the ether and alcohol mixture was boiled off at a very low temperature. When all traces of alcohol were gone, ether alone was added to the watery suspension of coagulated protein, and after ten minutes of gentle shaking in a separatory funnel, the ether was decanted. This was replaced by another volume of fresh ether, which, after the shaking had been repeated, was decanted. These two portions of ether when combined and evaporated to dryness contained within a few milligrams of the total amount of extractable fat of the specimen.

No such clearing as is worked by ether and alcohol combined can be done with petroleum ether and alcohol, for water will not mix freely with a mixture of petroleum ether and alcohol.

In trying to "shake out" the fat from these fluids and thereby dispel milkiness, we fail to remove fat because the fat solvent is not miscible with water (the continuous phase of the suspension), and therefore our solvent does not come in contact with the fat (the disperse phase). When the fat solvent can be made to mix with water, it removes fat

to current, the dissociation of salt liberated so much hydrochloric acid and sodium hydroxid that the change in H-ion obscured any migration of the suspension. To overcome this, the fluid was dialyzed sixty hours in a Graham dialyzer, with 200 volumes of distilled water changed twice. This usually diminished the salt content so that no reaction with  $\text{AgNO}_3$  could be obtained. During this process there was considerable precipitation and clumping, but, by vigorous shaking, a fine suspension could be obtained, much like the original. This was electrolyzed in cells of original design, so constructed that the substance electrolyzed was not affected by precipitation on electrodes or by precipitation from a change in H-ion, and the entire product could be removed for examination with no loss and no mixing.

In order to get a better suspension, the fluids were in some instances diluted to six volumes with water, so that sedimentation was not rapid enough to interfere with migration. At the end of the experiment, usually in twelve or twenty-four hours, the electrolytic cells were

*Summarized Results of Five Experiments*

$p_H$	Protein-Fat Ratio	Protein-Fat Ratio
	Positive Cell	Negative Cell
9	155 100	240 100
8	300 100	124 100
7	370 100	212 100
6	112 100	320 100
5	115 100	308 100
Control 9	396 100	376 100

separated by taking apart the rubber connections, the cells were shaken out, and the total solids and total fat were determined by continuous extraction. This was done at a  $p_H$  of 9, 8, 7, 6, 5, and the figures given herewith are the ratios of protein to fat in the positive and negative cells, respectively. If we assume that no other solids than protein and fat remained after dialysis, the ratio of protein to fat in each cell represents the degree of transportation by the electric current. The accompanying table gives the summarized results of five experiments.

When electrolysis was done at a  $p_H$  on the alkaline side of the iso-electric point of protein, both protein and fat migrated to the positive pole, making that cell very turbid and leaving the negative clear. When it was done at a  $p_H$  near the iso-electric point or at the acid side, fat continued to migrate to the positive, but protein went to the negative and both cells continued to be turbid. However, after adjusting both cells to their original  $p_H$  of about 9, the positive cell remained turbid and the negative one became much clearer. So far as electrolysis was capable of separating suspended protein from fat, it was likewise capable of dispelling turbidity in the former and concentrating it in the latter.

imens of considerable volume frozen in a cooling chamber at 18 F show more pellicle than do those frozen by carbon dioxid

"Cracking" the emulsion of these fluids by freezing resulted in distinct but not complete clearing. This is probably accomplished by the crystallization of water with attendant crowding together of the suspenoid. When colloid ice was formed by rapid freezing or by freezing accompanied by agitation, this "cracking" effect was wanting. Freezing did not completely clear these fluids, but greatly supplemented the clearing of sedimentation.

#### PEPTIZATION

Peptization was employed to reduce all protein to a simpler form that should not cause turbidity. When digested by proteolytic ferments—commercial pepsin and pancreatin—these fluids were not changed in appearance. The fermentation was controlled by digestion of suspended heat-coagulated protein and by the biuret test before and after digestion. It could be shown that, although digestion had gone to the peptone stage, there was no clearing of the specimen. Heat-coagulated protein of the control was completely cleared by the same ferment in the same time. Peptization of the white fatty residue obtained by filtration was tried with hydrochloric acid and pepsin. This rendered the mixture more fluid, but did not appreciably clear it, even though a peptone biuret reaction showed that protein had been well digested. Pancreatic fermentation of the same filtrate also made this residue more fluid and cleared it somewhat, and here digestion was shown to have split up all heat-coagulable protein, yet the clearing effect was very slight. It must be remembered that this same digesting probably split some of the fat into fatty acids and contributed to clearing in that manner.

Peptization of the whole fluid or of its concentrated milky substance did not clear these fluids, but peptization of the residue in an extraction thimble left a much clearer solution.

Peptization at best is difficult to carry completely to the peptone stage with protein. In these experiments, even though peptization was fairly complete, no clearing was noted so long as suspended fat was present, but when the fat was removed by extraction or by filtration and extraction combined, peptization cleared suspensions of the fat-free protein. This is offered as evidence that the milkiness is due to fat and to no protein substance.

#### ELECTROLYSIS

When these fluids were viewed under a dark-field microscope in an electric field, there was migration of the suspension, principally to the positive pole, but there was no constant and uniform direction of migration. When they were placed into an electrolysis cell and exposed

but at the same time coagulates protein, thus forming a new cause for milkiness as soon as the old one is dispelled. By careful manipulation these two steps can be separated long enough to permit a clear period between the solution of fat and the coagulation of protein, and this clearing is just enough to demonstrate that the original milkiness was due to fat.

That this solvent action of ether and alcohol is explained by so simple a matter as miscibility is doubted by Sollmann. He has observed the behavior of an oil-water system, with addition of ether and then of alcohol. He saw a distinct swelling of oil droplets after the addition of ether and a fusion of these droplets after the further addition of alcohol, which indicates that the solvent enters, but that surface forces prevent fusion of the solvated particles, and further, that alcohol lowers the surface tension so that solvated globules can fuse. It was also observed under the microscope by Dr. Sollmann that, on the addition of small amounts of calcium chloride to these fluids, the particles in suspension flocculated but did not fuse. This flocculation did not alter the gross appearance of the fluid materials, but did modify the rate and degree of ether extraction. In one instance, up to 35 per cent fat could be shaken out, with considerable clearing. The explanation of these phenomena is simplified if we accept the generally believed theory that these fat particles are surrounded by a thin film of soap, probably a sodium soap. In this case the calcium displaces the sodium and forms a calcium soap, which is less hydrophilic and, as seen by the clumping, more easily agglutinated.

Calcium soap films would presumably be more easily passed by ether than sodium soap films and would therefore be more easily shaken out. Furthermore, it can be presumed that, with a less hydrophilic soap membrane, there would be a rise in the solubility quotient  $\frac{\text{solubility ether}}{\text{solubility water}}$ , resulting in easier extraction. (One must also consider changes in solubility due to a modification of surface tension or surface charge when sodium soap has been displaced by calcium soap.)

#### FREEZING

Freezing is known to "crack" emulsions, and it was employed for that purpose. It coagulated a few flakes of protein and changed the general appearance very little, but if the specimen was centrifuged vigorously, a much wider and thicker creamy pellicle was brought up than was possible before freezing. Very little clearing could be noticed by freezing and centrifuging. If a specimen is centrifuged for one hour and all pellicle removed, and the process is repeated until none forms, this specimen, on being frozen and centrifuged again after thawing, will form a quite heavy pellicle and be appreciably cleared. This change is best accomplished by a slow process of freezing. Spec-

The filtrate from porcelain filtration when shaken with ether formed a heavy gelatinous mass similar to that of the whole fluid and prolonged exposure to ether removed no fat but left considerable coagulum in the otherwise clear filtrate, so that the fluid deprived of its turbidity and shaken with ether behaves in no way differently from the original. When shaken with a mixture of equal parts ether and alcohol, three of these fluids could be completely cleared (the two others were not tried), but this procedure had to be carried out with speed and care. As an ether-alcohol mixture, unlike ether alone, was freely miscible with watery ascitic fluid, it was a better extraction fluid, but employment of an excess of alcohol or prolonged exposure to dilute alcohol coagulated protein and obscured whatever clearing effect solution of fat might bring about.

This clearing was best done in test tubes with from 5 to 7 cc of the fluid to be cleared. An ether and alcohol mixture was added, 1 cc at a time, and vigorously shaken to accomplish mixing in the shortest time possible. Very quickly another cubic centimeter of the solvent was added and the tube quickly shaken. When approximately an equal volume of solvent has been added, the mixture suddenly clears and remains clear for a few minutes. It is never brilliantly clear, for small air bubbles are included, but before the protein coagulating effect of the alcohol begins there is a space of from a few seconds to a minute or two in which the solution of suspended fat is accomplished. When an excess of alcohol is added, milkiness returns and remains. If alcohol alone be added just short of the point where it will coagulate protein and then an excess of ether, a similar clearing results.

That fat solution is accomplished by this process was proved by adding ether and alcohol in excess, thus coagulating all protein. After this, the ether and alcohol mixture was boiled off at a very low temperature. When all traces of alcohol were gone, ether alone was added to the watery suspension of coagulated protein, and after ten minutes of gentle shaking in a separatory funnel, the ether was decanted. This was replaced by another volume of fresh ether, which, after the shaking had been repeated, was decanted. These two portions of ether when combined and evaporated to dryness contained within a few milligrams of the total amount of extractable fat of the specimen.

No such clearing as is worked by ether and alcohol combined can be done with petroleum ether and alcohol, for water will not mix freely with a mixture of petroleum ether and alcohol.

In trying to "shake out" the fat from these fluids and thereby dispel milkiness, we fail to remove fat because the fat solvent is not miscible with water (the continuous phase of the suspension), and therefore our solvent does not come in contact with the fat (the disperse phase). When the fat solvent can be made to mix with water, it removes fat

to current, the dissociation of salt liberated so much hydrochloric acid and sodium hydroxid that the change in H-ion obscured any migration of the suspension. To overcome this, the fluid was dialyzed sixty hours in a Graham dialyzer, with 200 volumes of distilled water changed twice. This usually diminished the salt content so that no reaction with  $\text{AgNO}_3$  could be obtained. During this process there was considerable precipitation and clumping, but, by vigorous shaking, a fine suspension could be obtained, much like the original. This was electrolyzed in cells of original design, so constructed that the substance electrolyzed was not affected by precipitation on electrodes or by precipitation from a change in H-ion, and the entire product could be removed for examination with no loss and no mixing.

In order to get a better suspension, the fluids were in some instances diluted to six volumes with water, so that sedimentation was not rapid enough to interfere with migration. At the end of the experiment, usually in twelve or twenty-four hours, the electrolytic cells were

*Summarized Results of Five Experiments*

$p_H$	Protein-Fat Ratio		Protein-Fat Ratio	
	Positive Cell		Negative Cell	
9	155	100	240	100
8	300	100	124	100
7	370	100	212	100
6	112	100	320	100
5	115	100	308	100
Control	396	100	376	100

separated by taking apart the rubber connections, the cells were shaken out, and the total solids and total fat were determined by continuous extraction. This was done at a  $p_H$  of 9, 8, 7, 6, 5, and the figures given herewith are the ratios of protein to fat in the positive and negative cells, respectively. If we assume that no other solids than protein and fat remained after dialysis, the ratio of protein to fat in each cell represents the degree of transportation by the electric current. The accompanying table gives the summarized results of five experiments.

When electrolysis was done at a  $p_H$  on the alkaline side of the iso-electric point of protein, both protein and fat migrated to the positive pole, making that cell very turbid and leaving the negative clear. When it was done at a  $p_H$  near the iso-electric point or at the acid side, fat continued to migrate to the positive, but protein went to the negative and both cells continued to be turbid. However, after adjusting both cells to their original  $p_H$  of about 9, the positive cell remained turbid and the negative one became much clearer. So far as electrolysis was capable of separating suspended protein from fat, it was likewise capable of dispelling turbidity in the former and concentrating it in the latter.



imens of considerable volume frozen in a cooling chamber at 18 F show more pellicle than do those frozen by carbon dioxide

"Cracking" the emulsion of these fluids by freezing resulted in distinct but not complete clearing. This is probably accomplished by the crystallization of water with attendant crowding together of the suspensoid. When colloid ice was formed by rapid freezing or by freezing accompanied by agitation, this "cracking" effect was wanting. Freezing did not completely clear these fluids, but greatly supplemented the clearing of sedimentation.

#### PEPTIZATION

Peptization was employed to reduce all protein to a simpler form that should not cause turbidity. When digested by proteolytic ferments—commercial pepsin and pancreatin—these fluids were not changed in appearance. The fermentation was controlled by digestion of suspended heat-coagulated protein and by the biuret test before and after digestion. It could be shown that, although digestion had gone to the peptone stage, there was no clearing of the specimen. Heat-coagulated protein of the control was completely cleared by the same ferment in the same time. Peptization of the white fatty residue obtained by filtration was tried with hydrochloric acid and pepsin. This rendered the mixture more fluid, but did not appreciably clear it, even though a peptone biuret reaction showed that protein had been well digested. Pancreatic fermentation of the same filtrate also made this residue more fluid and cleared it somewhat, and here digestion was shown to have split up all heat-coagulable protein, yet the clearing effect was very slight. It must be remembered that this same digesting probably split some of the fat into fatty acids and contributed to clearing in that manner.

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again each day until the fifth or sixth, when both dogs had to be killed on account of empyema and pneumothorax

These fluids were very milky, with considerable blood and exudate. On centrifuging, many cells were thrown down, and a thin creamy layer was formed. When the cells and cream were removed, the bulk of the fluid was "pseudochylous," but with a rather high protein content. The average fat content before centrifuging was 200 mg per hundred cubic centimeters. The averages after centrifuging were specific gravity, 1.050, total nitrogen, 900 mg per hundred cubic centimeters, total fat, 40 mg per hundred cubic centimeters.

When treated by further centrifuging, by sedimentation, filtering, heat coagulation, salting out, mutual precipitation, extraction of peptization, these fluids behaved in every respect like the pseudochylous fluids tested above, so far as their milkiness was concerned. This demonstrates that chyle can be the source for finely suspended fat such as is seen in pseudochylous fluids.

*In Vitro*—To synthesize fluids as accurately as possible, it is necessary to obtain a very finely divided suspension of oil, which may be added to perfectly clear ascitic fluid until the natural fluids are matched as to milkiness. The first attempt to secure such a synthetic fluid was made by dissolving cod liver oil in ether, 1.5 gm to 90 cc. This ether-oil solution was floated on the top of 1 liter of distilled water in a mixing cylinder and very vigorously shaken. This much ether mixes readily with a liter of water, leaving the oil finely divided and suspended. The suspension even with vigorous shaking is not permanent, and if not further treated soon settles out as a cream. Before settling took place, the mixture was twice run through an homogenizer at about 800 pounds' pressure. The homogenizer was of the Manton-Gaulin type, in which coarse oil suspensions are forced through the very narrow slit between a valve and a valve seat. Powerful electric pumps force the droplets through by breaking them into fragments. Before being homogenized, the suspension was scarcely turbid, but after homogenization it was very milky. Air was then bubbled through for several hours, and all traces of ether removed. After a week or more, a cream came up, and the milkiness was somewhat diminished. The underlying fluid was siphoned out, and remained unchanged several months. This fluid added to clear ascitic fluid made a good "pseudochylous" ascitic fluid. It contained about 50 mg of fat per hundred cubic centimeters, and 300 mg of protein.

A second water suspension was made with liquid petrolatum, but this mixture was not very stable and continued to form a cream, so that, after two months, there were in suspension but 5 mg of oil per hundred cubic centimeters, although the mixture was still quite milky in appearance. A third suspension was made from fat extracted from

## DIALYSIS

Dialysis of these fluids was of no assistance in examining the turbid substance. When thin collodion sacs were used, both protein and fat dialyzed through and both sides were turbid. Thick collodion films and parchment allowed salts to dialyze out, precipitating protein and fat, and clearing resulted.

## SUMMARY OF ANALYSES

Analyzed chemically, pseudochylous fluids are invariably found to be of the nature of protein-poor blood serum to which has been added a substance in no way foreign to blood serum but still causing turbidity. Emulsified fat was found in all the specimens here examined, and evidence was presented to prove that by proper methods fat can always be found.

By physical methods of analysis, such as filtration, freezing, electrolysis and sedimentation, no turbid substance could be isolated, but one could be concentrated and otherwise much restricted, and it was always found to be emulsified fat.

Microscopic examination showed oil globules wherever turbidity was concentrated, but in the main the turbid substance was so finely divided as to present colloid properties.

Physicochemical methods for the analysis of colloids, such as salting out and mutual precipitation, like purely physical methods, could not isolate but only concentrated the turbid substance, and here again it was found to be emulsified fat.

Selective solubility of proteins, as by peptization, did not dispel turbidity, but selective solubility of suspended fat, as by ether and alcohol, did dispel turbidity.

From these facts one may conclude that fat is the turbid substance. By recognizing the colloid nature of suspended fat, one is able to explain the difficulties that have prevented the acceptance of the fat theory, especially the difficulties in sedimenting, in shaking out and in salting out, for colloid fat is very different from fat in larger masses.

## SYNTHESIS

*In Vivo*—To prove that chyle may be the source of such minutely divided fat, milky effusions were produced in two dogs by making a thoracic duct fistula into the thorax. Five dogs were operated on only two successfully. The operation was in two stages. By the preliminary one, the duct in the neck was tied off, and by the main one, two days later, a rib was resected and a section of the duct excised, so that a fistula was produced. The day following the operation, several hundred cubic centimeters of bloody, milky fluid were obtained, and

natural fluid containing this amount was more turbid. No oil could be made to pass a porcelain filter, and as much as 80 mg per hundred cubic centimeters of cod liver oil suspension would stand centrifuging indefinitely without settling out. Peptization and heating to the boiling point with acid had no effect, there being no protein present. Salting out with ammonium sulphate at one-half saturation always cleared all three systems, and salting to less than one-half saturation would clump up the particles to form a watery layer on top. Salting with saturated sodium chlorid in the presence of acid cleared them completely, as did mutual precipitation with any positively charged colloid, if used in proper amount, as determined by trial. Extraction by shaking with ether, even when long continued, did not clear any but the mineral oil systems and then not completely, but shaking with ether and alcohol mixture cleared them all three completely and instantly. Freezing when done gradually cleared them, but if it was done rapidly, especially if the tubes were agitated while freezing, the clearing was not complete. Electrolysis always caused these suspensions to migrate completely to the positive pole in acid or alkaline mediums.

From these results, it can be seen that suspended fat, even when not very finely divided, can account for milkiness that will not filter out with paper, will not settle out by gravity and will not shake out with ether alone, but will salt out, and these were the principal arguments whereby turbidity was ascribed to protein and the term pseudochylous came to be introduced.

#### ADSORPTION OF PROTEIN

Although it is not essential to an investigation into the milkiness of these fluids, it is interesting to speculate what relation there may be between fat and protein in either the natural fluids or the synthetic. When fats and protein are both in an alkaline medium and hence freely suspended, there may be no relation other than that of two separate dispersoids in the same continuous phase. The great difficulty found in separating them may be due altogether to the similarity of their properties as colloids in suspension.

When the two substances are collected together from their watery medium, they are never found in constant ratios, as can be seen by making total nitrogen determinations on measured amounts of precipitate removed by filtration, heat coagulation, salting out or electrolysis. This militates against any chemical union of the two substances.

The physical relation of adsorption must be considered, for it is a property common to colloids in suspension to adsorb substances. Adsorption probably takes place when acidulation or heat coagulation removes both these substances from suspension, but then we have altered

natural ascitic fluid, simple shaking being relied on, without homogenization, which requires very large volumes on account of the capacity of the machine. This suspension was stable at 100 mg per hundred cubic centimeters, and was very milky.

All three synthesized fluids resembled the natural very closely in gross appearance, but microscopically the fat particles were very much larger, and the addition of protein did not alter their size, arrangement or brownian movement. When these fluids were tested by the methods used on the natural fluids, very few differences were noted, and none of them were in essentials. Filtering through paper removed nothing from any specimen except from the one made with mineral oil. In this one, the fat particles were largest, but filtering through porcelain removed all fat. Sedimentation except in the mineral oil system removed nothing either up or down, but heat coagulation with weak acids completely cleared them all. Salting out showed the same clearing effects as in the natural fluids, whenever any globulin was precipitated, fat was also precipitated, and clearing resulted. Mutual precipitation reactions were also the same as in the natural fluids, fat was precipitated by any colloid bearing a positive charge, and whenever globulin was precipitated, fat was likewise precipitated. As in the natural fluids, very slight acidulation, just sufficient to go beyond the iso-electric point of serum albumin, gave marked flocculation but not complete clearing. Extraction gave the same results as before, but simple shaking with ether partly cleared the mineral oil system. Shaking with ether removed no fat from the cod liver oil system, but ether and alcohol cleared it promptly. Freezing partly cleared all three systems by precipitating protein and causing cream to come up. Peptization partly cleared both the cod liver oil and the natural human fat systems, but did not affect the mineral oil system. Electrolysis showed a concentration of fat always to the positive pole, and in an alkaline medium a concentration of protein to the negative, but it never accomplished a complete separation.

To summarize the results of examining these synthetic fluids, it must be said that they differ from the natural only in minor points, and the difference can be largely accounted for by poor homogenization, for no artificial means tried here could break up oils and fats into such small particles as naturally occur. In synthetic fluids, fat alone can cause milkiness.

In order to determine what rôle fat alone might play in determining the physical characteristics of milky fluids, simple oil-water systems of cod liver oil, mineral oil and human fat, made as described above, except that no ascitic fluid or other protein was added, were examined, with the following results.

Milkiness, as determined by reading print through tubes, was quite marked with as low as 20 mg per hundred cubic centimeters, but a

## WATER INTOXICATION \*

LEONARD G ROWNTREE, M D

ROCHESTER, MINN

Strange as it may appear, little or nothing is known concerning the effects of an excessive intake of water. Statements such as "even water must be toxic" are heard almost daily, yet the toxicity attending excessive ingestion of water has been taken for granted rather than proved. So far as I am aware the symptoms of water poisoning and the mode of death in water intoxication have never been determined. This is due, in part, to the fact that quantities in excess of those taken voluntarily are necessary for its production, and that the rôle of water intoxication in pathologic conditions has not as yet been fully appreciated.

Nature has provided adequately against water intoxication. The sensation of satiety following the ingestion of small or moderate quantities of water renders the subsequent ingestion of larger amounts increasingly difficult. The pylorus prevents the sudden or immediate egress of large volumes of water, and consequently excessive ingestion results in gastric distention, which is followed in man, and in certain animals, by regurgitation and vomiting. In some animals diarrhea results. Water is an extremely effective diuretic. Absorption of large quantities promptly induces diuresis which prevents accumulation in the body. Thus, the factor of safety is great.

### THE TOXICITY OF WATER FOR LOWER ORDERS

The toxicity of pure, fresh and distilled water for the lower orders of life, especially for fish, for isolated organs, for unicellular organisms and for certain cells, has been the subject of many investigations since the time of Paul Bert,<sup>1</sup> who, in 1866, ascribed the toxic effect of fresh water for the mullet to the difference in osmotic pressure between fresh water and sea water, causing the tissues to absorb water in excess. Plateau,<sup>2</sup> in 1871, ascribed the toxic effect of fresh water for marine crustaceans to the diffusion of salts from the organism, an explanation

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\* From the Division of Medicine, The Mayo Foundation.

\* The word "intoxication" as used here designates poisoning and has no reference to alcohol intoxication.

1 Bert, P. Note sur la mort des poissons de mer dans l'eau douce. *Mem de la soc d sc phys et Naturelles d Bord*, 4 47-49, 1866.

2 Plateau, F. *Recherches physico-chimiques sur les articules aquatiques*, *Mem d l'acad Roy d Belgique* 36, 1870. Quoted by Bullot.

the protein by reversing the electric charge from negative to positive, while the fat remains unchanged. A fusion in the nature of adsorption then occurs between particles.

In the synthesized milky fluids that remain stable, there was no adsorption demonstrable. This was tested by two experiments.

Protein was added to a supersaturated oil-water system before any oil had settled out. After twenty-four hours, when a heavy cream had come to the top, the cylinder, which was 15 cm. long and held 100 c.c., was pipetted into two halves, an upper and a lower, and a nitrogen determination was made on equal amounts of top and bottom, discarding, by way of precaution against protein sedimentation, the very bottom 2 or 3 c.c. The total amounts of nitrogen on top and on bottom were almost equal, showing no concentration of protein at the top. By this process of "flotation," it was expected that protein, if adsorbed to fat particles, would be concentrated at the top with the fat, but there was no concentration.

The problem was approached from another angle by adding protein to a watery suspension of cod liver oil that had been deprived of all cream by settling and siphoning, and had been homogeneous for a long time. This procedure determined the maximum size at which fat particles could stay free in suspension. Blood serum was then added, the protein in which was free to be adsorbed to the fat particles and thereby augment their size above the maximum, so that a cream should develop. After a week, no cream had come up, nor was the turbidity increased.

While neither of the foregoing is a critical experiment, they are cited as evidence against adsorption of protein to fat. Whether any substances other than protein may be adsorbed to fat particles need not be considered in this investigation, but there is a possibility of soap in this rôle. While no soap could be discovered, it may still be present in quantities sufficient to form a surface film over particles of fat. This is suggested by the fact that mineral oil, which cannot saponify when suspended in pure water, made a much less stable system than did cod liver oil or human fats, both of which may be saponified by the alkali present in the serum, and it is further suggested by the phenomenon seen on the addition of calcium and noted above under extraction.

#### SUMMARY AND CONCLUSIONS

Five so-called pseudochylous fluids examined chemically were found to be protein-poor blood serum made turbid by some unknown substance. This substance was found by selective solubility, partial isolation, concentration and other restriction to be emulsified fat, so finely divided that it had assumed properties common to colloids.

By operating on the thoracic duct, dogs were made to develop pseudochylous fluids from chyle.

Pseudochylous fluids were synthesized from oil-water mixtures.

By recognizing the colloid properties of suspended fat, we discover the fallacies whereby the term pseudochylous originated. The term pseudochylous is misleading and should be discarded.

latter ascribing the toxicity encountered to the properties of distilled water itself. He also found that the addition of sodium chlorid suppressed this toxicity. Sufficient sodium chlorid to yield 8 100,000 molecular salt solution sufficed to overcome the toxic properties of distilled water.

#### TOXICITY RESULTING IN MAN FROM EXCESSIVE INGESTION OF WATER <sup>12</sup>

Excessive ingestion of water is rarely encountered clinically in health or in disease, except, perhaps, in certain febrile diseases and in diabetes insipidus. In health, possibly, the largest amounts have been ingested in experiments concerned in investigations of the physiology of diuresis. Thus, in the experiments of MacCallum and Benson <sup>13</sup> as much as 2,500 c c was ingested in the course of two hours and the output of urine reached 20 c c each minute. Priestley <sup>14</sup> drank two liters of water within fifteen minutes. In one experiment he took 5,500 c c of fluid within six hours. During the same period he passed 5,460 c c of urine. Diuresis reached the rate of 1,200 c c each hour with a total output for a single hour of 888 c c. Amberg and Austin, <sup>15</sup> in the study of skin elasticity, imbibed three liters of water within twenty minutes. Amberg says that elastometric measurements could not be made because of the development of tremor and muscle twitching.

In typhoid fever large quantities of water, five, six or even from eight to twelve liters each day, have been and are still used at times without the appearance of untoward symptoms. Miller and Williams, <sup>16</sup> on administering water up to ten liters each day to patients suffering from chronic nephritis and hypertension, noted marked increase of blood pressure, headache, dizziness, restlessness, chills, fulness of the abdomen, vomiting, dyspnea, cramps in the legs, and marked increase in weight. These results are in striking contrast with the entire absence

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<sup>12</sup> Pure water, as distinguished from distilled water, has been studied by Kohlrausch and Heydweiller. From the standpoint of electrical conductivity, water purer than distilled water may be obtained from freshly melted ice from glaciers in high mountains. According to Hans Koeppé (*Reines Wasser seine Giftwirkung und sein Vorkommen in der Natur*, *Deutsch med Wchnschr* **24** 624-626, 1898), such pure water does not slake the thirst and is inherently toxic, leading to vomiting and gastric catarrh. However, he furnishes no details relative to this toxicity.

<sup>13</sup> MacCallum, A. B., and Benson, C. C. On the Composition of Dilute Renal Excretions, *J Biol Chem* **6** 87-104, 1909.

<sup>14</sup> Priestley, J. G. The Regulation of Excretion of Water by the Kidneys, *J Physiol* **1** 304-311, 1916.

<sup>15</sup> Amberg, S., and Austin, R. S. Personal communication.

<sup>16</sup> Miller, J. L., and Williams, J. L. The Effect on Blood Pressure and the Nonprotein Nitrogen in the Blood of Excessive Fluid Intake, *Am J M Sc* **161** 327-334, 1921.



given by J Loeb<sup>3</sup> for the same phenomena which he observed in his studies on a marine gammarus

The toxicity of distilled and of fresh water for lower species was a topic of lively discussion toward the close of the last century Ringer and his collaborators,<sup>4</sup> in a series of papers published from 1883 to 1894, held that distilled water was strikingly toxic for the goldfish, the minnow, the stickleback, the eel, the newt, the tadpole, the egg of the frog and for a fresh water worm, *Tubifex vivulorum*. He demonstrated that distilled water caused the disappearance of ciliary motion in less than twenty-four hours in the vibratile epithelium of the gills of the anadon. He ascribed toxicity of distilled water to (1) subtraction from the organism of salts essential to life, (2) penetration of water into cells according to the laws of osmosis, and (3) imbibition of water by intercellular substances. But in 1893, there appeared a posthumous publication of a paper written by Naegeli<sup>5</sup> in which he proved that in his series of experiments traces of copper in the water were the sole cause of death for the fresh water alga, *Spirogyra*. These traces were carried over from the still during distillation. It was found that copper in dilution of 1 77,000,000 sufficed to kill Locke,<sup>6</sup> in 1895, repeated some of these studies and showed that water distilled from and kept in glass is innocuous for tadpoles and *Tubifex vivulorum*. Ringer,<sup>7</sup> in 1897, confirmed these findings. The lack of toxicity of distilled water for the paramecium was demonstrated by Jennings<sup>8</sup> in 1897, for the young trout and tadpole by Moore<sup>9</sup> in 1900, and for a fresh water planarian, *Planaria maculata*, by Lillie<sup>10</sup> in 1900.

On the other hand, the toxicity of distilled water for the fresh water gammarus has been definitely proved by Loeb and by Bullot,<sup>11</sup> the

3 Loeb, J. Ueber die relative Giftigkeit von Destillirtem Wasser, Zuckerlosungen und Losungen von einzelnen Bestandtheilen des Seewassers fur Seethiere, Arch f Physiol **97** 394-409, 1903

4 Ringer, S, and Phear, A. G. The Influence of Saline Media on the Tadpole, J Physiol **17** 423-432, 1894

5 Nageli, C. Ueber oligodynamische Erscheinungen in lebenden Zellen, mit einem Vorwort von S. Schwendener und einem Nachtrag von C. Cramer, Denkschriften d Schweiz Naturforsch Gesellsch **33**, 1893. Quoted by Locke.

6 Locke, F. S. On a Supposed Action of Distilled Water as Such on Certain Animal Organisms, J Physiol **18** 319-331, 1895

7 Ringer, S. The Action of Distilled Water on *Tubifex*, Proc Phys Soc, J Physiol **22** 14-15, 1897

8 Jennings, H. S. Studies on Reactions to Stimuli in Unicellular Organisms. I. Reactions on Chemical, Osmotic and Mechanical Stimuli in the Ciliate Infusoria, J Physiol **21** 258-322, 1897

9 Moore, A. Further Evidence of the Poisonous Effects of a Pure Sodium Chlorid Solution, Am J Physiol **4** 386-396, 1900

10 Lillie, F. R. Some Notes on Regeneration and Regulation in Planarians, Am Naturalist **34**, 1900. Quoted by Bullot

11 Bullot, G. On the Toxicity of Distilled Water for the Fresh Water Gammarus. Suppression of This Toxicity by the Addition of Small Quantities of Sodium Chlorid, California University Publication, Physiology **1** 198-217, 1904

## THE EXPERIMENTAL INDUCTION OF ACUTE WATER INTOXICATION IN MAMMALIANS

Considering it likely that water was responsible for the intoxication and that pituitary extract favored its development through lessening the rate of excretion and lowering the rate of water exchange, or through rendering easier its escape from the vascular system into the tissues, I continued the research. In this series of experiments water was administered at a more rapid rate, that is, 50 cc of water for each kilogram of body weight every half hour instead of every hour, as in the earlier experiments. This amount insures an intake of water greater than the capacity of the organism to excrete it. The adoption of this simple modification in technic has proved very efficacious and has regularly resulted in the development of the manifestations of water intoxication. Tap water<sup>19</sup> or distilled water (from blocked tin or glass), irrespective of its temperature, has proved equally toxic. Water intoxication has been produced in dogs, cats, rabbits and guinea-pigs.

Water was administered readily to all of these animals through the use of an appropriately sized stomach tube and the mouth gag. For guinea-pigs, the ureteral catheter answered admirably. The handling of cats and rabbits is simplified through the use of the box method employed by Keyser<sup>20</sup>. Prior to the administration of water, the weight and temperature of the animals were taken. This was repeated at the onset of convulsions and again at the close of the experiment. In all experiments, water was administered at intervals of one-half hour. In the interim the animals were removed from the box, placed in a cage or on the floor and kept under careful observation. Subsequent to the development of convulsions they were returned to their cages, except when death seemed imminent, under which conditions observations were continuous. A necropsy was performed as soon after death as possible.

## THE MANIFESTATIONS OF WATER INTOXICATION IN VARIOUS ANIMALS

Reference has been made to the character of the symptoms of water intoxication encountered in animals subsequent to the administration of pituitary extract. Generally speaking, the clinical picture is much the same whether or not pituitary extract is used. However, in animals

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19 An analysis was made March 4, 1920, by the Minnesota State Board of Health of the water supply of Rochester, Minn. The report states "The field survey shows conditions which are satisfactory from a sanitary point of view, and in the analytical results indications of contamination were not found. The water from this supply can be considered safe for public consumption."

20 Keyser, L. D. A Box for Handling Small Animals in the Laboratory, J. Lab. & Clin. M. 7 761-762, 1922.

of symptoms in patients with diabetes insipidus who ingest similar amounts. In this disease, the rate of water exchange is high, not infrequently at a higher level than from 10 to 12 liters each day, and it may be maintained at this level for months or years without the appearance of untoward symptoms, such as are seen in water intoxication. In Trousseau's<sup>17</sup> case, the highest rate of water exchange on record, the urinary output was 43 liters each day, and the water intake 40 liters. With the water balance set at this almost unbelievable level, no signs of water intoxication developed, probably because of the prompt elimination of water. In all probability it is not the quantity of water ingested or the rate of water exchange, but rather an intake in excess of the ability of the body to excrete, that is, a positive balance with water accumulation in the body, which is responsible for the development of water intoxication. On the other hand, it may be due to the excess of water robbing the body of salt.

#### WATER INTOXICATION SUBSEQUENT TO THE ADMINISTRATION OF PITUITARY EXTRACT

Recently Larson, Weir and Rowntree<sup>18</sup> called attention to the peculiar form of intoxication resulting from the excessive intake of water subsequent to subcutaneous administration of pituitary extract. Three patients with diabetes insipidus, after receiving pituitary extract subcutaneously, continued to take water in the amounts to which they had become accustomed, that is, at the rate of from 8 to 10 liters each day. Within a few hours, headache, nausea, asthenia, incoordination and staggering gait developed and in one instance slight subcutaneous edema. The toxic manifestations were extremely severe and in one instance became alarming and occasioned grave concern to those in attendance.

Owing to the severity of the reaction in man, experiments were carried out solely on animals. Water intoxication was readily induced in dogs through excessive ingestion of water subsequent to the subcutaneous administration of pituitary extract. The symptoms of poisoning were asthenia, restlessness, frequency of urination, diarrhea, salivation, nausea, retching, vomiting, tremor, muscle twitching, ataxia, convulsions, frothing at the mouth, stupor and coma, ending in death in a large proportion of the animals. In reporting this work, the authors asserted that this intoxication could not be induced by pituitary extract alone or by water alone, but only by the combination of the two.

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17 Trousseau, A. *Lectures on Clinical Medicine*. London: Hardwicke, 1867.

18 Larson, E. E., Rowntree, L. G., and Weir, J. F. *Studies in Diabetes Insipidus, Water Balance, and Water Intoxication*, *Arch. Int. Med.* **29**: 306-330 (March) 1922.

development of this intoxication in a dog and its disappearance under sodium chlorid solution

In cats suffering from water intoxication, retching is violent but vomiting is infrequent. In fact, convulsions often develop during, or soon after, the beginning of the first spell of retching or vomiting. Diarrhea is common. Stupor is marked. Convulsions are, perhaps, somewhat less violent than in dogs and are succeeded, as a rule, by asthenia and stupor. If animals survive they appear to be normal within a few hours (Table 2)

TABLE 2—WATER INTOXICATION IN A CAT

Time	Weight, kg	Water Intake, C c	Temperature, C	Remarks
8 45 a m	3 0	125	36 5	
9 15 a m		125		
9 45 a m		125		
10 15 a m	3 4	125		Vomited
10 45 a m		125		
11 15 a m		125		Salivated
11 45 a m		125		Vomited
12 15 p m		125		
12 45 p m	3 5	125	37 0	Ataxic
1 15 p m		125		
1 45 p m		125		
2 15 p m	3 7	125	37 0	
2 45 p m		125		
2 48 p m				Typical convulsion, head retracted, running movements of legs, eyes dilated, respiration shallow and rapid, and asthenia and stupor
2 55 p m				About 15 cc fluid obtained with stomach tube, death during night

TABLE 3—WATER INTOXICATION IN A RABBIT

Time	Weight, Kg	Water Intake, C c	Temperature, C	Remarks
9 30 a m	1 7	100	36 5	Distilled water at body temperature
10 15 a m		100		Normal
11 15 a m		100		
11 45 a m		100		
12 00 m	2 1			Salivated, ataxic convulsions lasting two minutes
12 15 p m	2 1		37 0	
1 05 p m	2 1			Found dead

In rabbits, retching and vomiting are usually absent. They develop a staggering gait, become asthenic, eventually lie down and become very sick. Diarrhea is absent, as a rule, but diuresis is marked and salivation is common. Stupor develops rather than coma. The convulsions approach in violence those occurring in the dog. Death may occur during either convulsions or stupor (Table 3)

In guinea-pigs, retching and vomiting do not develop, they have diarrhea, salivation and marked diuresis, become markedly ataxic and

under the influence of pituitary extract, irritability of the bladder and bowels is more common, as evidenced by more frequent and more ineffectual attempts at urination and defecation. Some form of nervous and mental excitation also develops, as evidenced by restlessness, aimless activity and constant running about. Under the influence of pituitary extract, coma is apparently somewhat deeper and convulsions are more pronounced, although this is difficult to prove.

In dogs, the symptoms of water intoxication consist of asthenia, restlessness, frequency of urination, nausea, retching, vomiting, salivation, muscle twitching, ataxia, tonic and clonic convulsions associated with frothing at the mouth and stupor or coma, ending in death or complete recovery within a few hours. Early in the intoxication, the

TABLE 1—WATER INTOXICATION IN A DOG (F10)

Time	Weight, kg	Water Intake, Cc	Temperature, C	Remarks
A 9 10 a m	5.5	250	37.5	Lively and vivacious
9 40 a m		250		
10 20 a m		250		
10 40 a m		250		Diarrhea, vomiting, quiet and depressed, and ataxic on walking
11 10 a m		250		
11 40 a m		250		
12 30 p m		250		Salivated, vomiting, convulsions, followed by stupor, weakness, flaccidity, abject helplessness
1 45 p m	6.0			
B 1 50 p m				55 cc 10 per cent sodium chloride solution stool immediately after injection, shook himself and lay down quietly
2 00 p m				
3 00 p m			38.0	Walks, markedly improved salivation disappeared, voids profusely
5 00 p m	5.6			Apparently normal

animals often attempt to hide in a corner, later they lie down and become apprehensive and watchful. As a rule, the convulsions resemble those of strychnin in their severity and may recur repeatedly at intervals of a few minutes. In the period between convulsions, a state of extreme asthenia, stupor or coma supervenes. Although deep coma is encountered at times, more often the eyes are open and the animal is in a state of profound asthenia and abject helplessness, accompanied by complete flaccidity. The animal may lie on its side, or occasionally on its abdomen, with its legs stretched out, and for periods as long as five minutes they remain absolutely quiet, without movements of any kind. During this period the pulse and respiration remain normal, but in marked intoxication marked bradycardia often develops. In several instances a pulse of 50 or 60 was present. Arrhythmia developed in one or two instances. In the event of recovery, all abnormal manifestations disappeared within from twelve to eighteen hours. Table 1 shows the

## CHANGES IN WEIGHT AND THEIR INTERPRETATION

Difficulty is encountered in ascertaining the true significance of the increases in weight. Obviously, it is impossible, prior to the administration of water, accurately to determine the amount of fluid present in stomach and intestines.<sup>20a</sup> The weight indicated at any time during an experiment, or at the end, represents total weight only, and fails to differentiate between water assimilated and that which still remains in the gastro-intestinal tract. The stomach tube may reveal the amount of water in the stomach and whether or not there is sufficient to occasion gastric distension.

TABLE 6—WATER INTOXICATION IN CATS, RABBITS AND GUINEA-PIGS

Rabbit	Weight, Kg	Water, Cc	Time, Hours	Gain in Weight, Kg	Increase, per Cent	Remarks
1	1.9	700	5.25	0.5	26.3	Typical convulsions, died next night
2	2.5	500	4.50	0.3	12.0	Convulsions, recovered
2	2.5	500	3.42	0.2	8.0	Convulsions, recovered
3	1.7	400	3.58	0.3	17.6	Convulsions, died
Guinea-pig	Gm			Gm		
1	513	220	3.42	269	52.2	Convulsions, died, weight at death 782 gm
2	771	220	5.00		19.8	Convulsions, died, weight at death 924 gm
3	515	90	2.00	50	9.7	Convulsions, died, 25 cc of fluid
4	490	200	3.00	105	21.0	Convulsions, died
5	510	215	2.45	98	19.00	Convulsions, died, 20 cc of fluid
Cat	Kg			Kg		
1	3.9	1,250	5.00	0.1	2.56	Convulsions, died
2	3.0	1,725	6.00	0.7	23.3	Convulsions, died
3	2.9	1,200	5.00	0.7	24.0	Convulsions, recovered
3	2.8	800	3.33	0.6	21.0	Convulsions, died
4	2.4	500	2.00	0.3	12.0	Convulsions, died
5	1.8	1,400	7.25	0.9	50.0	Convulsions, died
6	3.1	700	3.58	0.7	22.0	Convulsions, recovered
7	3.0	900	4.50	0.6	20.0	Convulsions, recovered

In many instances the water content of the intestines was determined at the necropsy, but owing to the fact that the amount in the intestines prior to the administration of water was not known, these figures are of but limited significance.

## EXPERIMENTAL INDUCTION OF SUBACUTE WATER INTOXICATION IN RABBITS

Subacute water intoxication can readily be induced in rabbits. Water up to one-fourth of the body weight, given daily by stomach tube and in divided doses,<sup>3</sup> is tolerated over periods of from two to three weeks without evidence of untoward symptoms. Water in amounts of from 300 to 333 cc for each kilogram of body weight daily results, in the course of from one to two weeks, in the development of subacute water intoxication (Table 7).

<sup>20a</sup> Under proper preliminary conditions intestinal content of water may be rather uniform. Stomach contents may be removed before starting the experiment. Hence these difficulties may, perhaps, not be insurmountable.

spread their legs in a peculiar manner in an effort to support the body. They find great difficulty in walking, and often roll on their sides, the legs exhibiting marked running movements. Abdominal distention, as a rule, is marked. Stupor and convulsions ensue earlier and are more common than in larger animals (Table 4).

#### THE RELATIVE EASE OF INDUCING CONVULSIONS IN VARIOUS ANIMALS

In each species great variations are encountered with regard to individual susceptibility, that is, the readiness with which convulsions

TABLE 4—WATER INTOXICATION IN A GUINEA-PIG

Time	Weight, Gm	Water Intake, C c	Remarks
9 40 a m	771	20	Normal
10 30 a m		20	
10 55 a m		20	
11 25 a m		20	
11 55 a m	891	20	Normal
12 15 p m		40	
1 10 p m			Salivation
1 25 p m		40	
2 05 p m		40	
2 20 p m			
2 55 p m	924		Convulsion
3 10 p m			Regains feet but cannot walk, feet spread out in attempts to walk Weight at death 924 gm, an increase of 153 gm nothing in stomach at necropsy, edema of lungs

TABLE 5—WATER INTOXICATION IN DOGS

Dog	Weight, Kg	Water, C c.	Percentage of Body Weight	Time Elapsing	Gain in Weight, kg	Per centage Increase	Remarks
3	6.2	3,000	48.2	4 hours,	0.4	6.6	Convulsions, recovered
4	6.3	3,900	62.0	50 minutes 6 hours,	0.7	11.1	Died
5	7.1	5,250	83.0	30 minutes 8 hours	0.4	5.6	Recovered, experiment repeated the next day
5	6.9	2,450	35.5	3 hours	0.5	7.2	Convulsions, water continued weight at death, 8.4 kg, drained 625 c.c. fluid from stomach and intestines
6	4.4	2,800	63.6	5 hours, 45 minutes	0.5	7.6	Water continued 6.75 c.c., died, weight at death, 5.1 kg

occur. In the dog, vomiting unquestionably tends to postpone the onset of convulsions. To a lesser extent this is also true of the cat. In rabbits and in guinea-pigs the water ingested is practically all assimilated and hence water toxicity develops somewhat earlier. Occasionally, individual dogs are markedly resistant to water intoxication. This may be due to recent access to an abundant supply of salt. Table 5 presents the important data for a group of dogs and Table 6 for cats, rabbits and guinea-pigs.

vening in the course of the stupor, coma or asthenia. A condition of stupor or coma may persist for three or four days prior to the death of the animal. Recovery may follow discontinuance of water excess.

#### NOTES ON THE PATHOLOGIC FINDINGS IN ANIMALS WITH ACUTE WATER INTOXICATION

Dr. Robertson has studied the tissues from several of these animals and submits the following report:

Results of postmortem studies on the animals used for experimentation, with a few exceptions, have revealed a notable absence of any specific pathologic changes. Such a result might reasonably be expected. The fulminating character of the clinical phenomena both in the rapidity and violence of their course strongly suggests such a speedy alteration in the metabolic activities of the vital cells of the body that few or no changes in the physical appearances of the cells or tissues can be detected. Pertinent analogies to this conclusion are presented by definite organic intoxications which produce alterations in structure only in inverse proportion to the time element and rarely in direct proportion to the violence of the symptoms.

At the first two examinations made on dogs who had succumbed to violent convulsions in a few hours, the only striking change that could be noted was a marked edema of the connective tissues around the portal vein and the area of distribution of its larger branches within the liver. The liver, itself, presented on section a moist surface as did also the kidney and there was slight edema of the upper portion of the mesentery. There was no marked increase of fluid on the surface of the brain although the brain itself was distinctly moist.

Microscopic examination of these tissues only served to emphasize the gross appearances. There was no definite edema of cells in the kidney, brain or liver, and no definite microscopic alterations could be identified. The connective tissues in the cortices of the kidneys, around the distribution of the portal vein, particularly its larger branches, and around the vessels of the brain showed distinct edema. In the two first cases this edema was marked in the substance of the liver.

Succeeding postmortem examinations on both rabbits and dogs were surprising because of the lack of consistency in the findings. Occasionally, the edema was again distributed as just indicated, but often it was almost entirely confined to the kidney, although there were always definite signs of increase of fluid within the brain substance. Uniformly in all cases the kidney was abnormally moist and microscopically showed evidences of interstitial edema, but careful study of the cells did not reveal in any instance significant or uniform change.

In this connection it is interesting to note that the same appearance of excessive moisture in the pulp of the kidney and liver has been observed in human postoperative cases when the fluid intake had been pushed evidently beyond the ability of the patient's excretory capacity.

#### DISCUSSION

Although the amount of water administered is extremely large in most instances, the gain in weight is, by contrast, strikingly small. There is adequate provision against too great absorption. A large water intake results in free diuresis and, in dogs and sometimes in cats, in profuse vomiting. In order to produce the severe intoxication, an intake of



In the rabbit, the symptoms of subacute poisoning do not differ essentially from those of acute poisoning. Salivation first appears and this is accompanied by listlessness or lack of liveliness and often by ataxia, diuresis is marked and continuous, but the stools retain their normal consistency and their pellet-like form. The animal huddles into a corner and exhibits no interest in its surroundings. Weakness

TABLE 7—CHRONIC WATER INTOXICATION IN RABBITS

Rabbit	Date, 1922	Weight, Kg	Water Intake, C c	Urine Output, C c	Remarks
6-B	4/26	2.9	675	675	250 c c for each kilogram a day in three doses
	4/27		675	675	
	4/28		675	675	
	4/29		675	640	
	4/30		225	300	
	5/ 1		675	665	
	5/ 2		675	650	
	5/ 3		675	600	
	5/ 4		675	625	
	5/ 5		675	600	
	5/ 6		675	640	
	5/ 7		225	270	
	5/ 8	3.2	870	775	Dose increased to 300 c c for each kilogram a day
	5/ 9		870	810	
	5/10		870	850	
	5/11		870	800	
	5/12		870	820	
	5/13		870	800	
	5/14		290	275	
8-B	5/15	2.9	290		Salivated Markedly salivated ataxic Convulsions at 9:30 a m, apparently recovered but died next night, no evidence of pneumonia at necropsy
	5/ 6		540	500	225 c c for each kilogram a day in three doses
	5/ 7		180	200	
	5/ 8		870	800	Dose increased to 300 c c for each kilogram
	5/ 9		870	790	
	5/10		870	800	Possibly slight salivation
	5/11		870	795	
	5/12		870	850	
	5/13		870	815	
	5/14	3.1	290	300	Salivated Markedly salivated and ataxic
9-B	5/15				Animal found dead in the morning with every indication of having died in convulsions, head retracted, no signs of pneumonia found at necropsy
	5/ 6	2.1	495	450	About 225 c c for each kilogram a day in three doses
	5/ 7		165	180	
	5/ 8		630	300	Dose increased to 300 c c for each kilogram a day
	5/ 9		630	300	
	5/10		630	600	
	5/11		630	590	
	5/12		630	610	
	5/13		630	600	
	5/14		210	200	
	5/15		630	595	
	5/16		630	600	
	5/17		630	600	
	5/18		630	590	
	5/19	2.4	210		Salivated and stupid convulsion and death at 2 p m, no evidence of pneumonia at necropsy

becomes marked and a state of stupor supervenes. Convulsions, similar in every respect to those of acute water poisoning, develop. The head is markedly retracted and this position may persist even after death. Subsequent to the convulsions, weakness progresses and helplessness becomes extreme. The animal may lie for an hour at a time on its side without moving. Micturition becomes involuntary. Death may occur suddenly during convulsions, or may come on gradually, super-

absorption of digestive products from the gastro-intestinal tract, dogs were first subjected to water abstinence experiments. The animals were subjected to two and four day periods of water fasting after which the intoxication was produced, attention being given to the ease with which it developed. In other experiments, an excess of water, 1,500 c c each day, was given for two day periods prior to the introduction of toxicity. The results of these experiments are set forth in Table 8. As far as these experiments go there is no evidence of absorption of toxic substances from the gastro-intestinal tract.

*The Rôle of the Liver* <sup>21</sup>—Inasmuch as at necropsy the liver showed evidences of edema, it seemed desirable to determine whether or not the liver played an important part in this intoxication. Consequently,

TABLE 8—EFFECT OF PREVIOUS FASTING WATER ABSTINENCE AND WATER EXCESS ON THE DEVELOPMENT OF WATER INTOXICATION IN DOGS

Dog	Weight, Kg	Water, C c	Time, Hours	Gain in Weight, Increase, kg per Cent		Remarks
14	4.4	2,700	5.75	0.5	11.3	Died, weight 5.1 kg, fluid in stomach 175 c c
15	6.8	3,750	7.00	0.5	7.6	Fasted two days, convulsions, recovered
15	5.6	3,850	7.16	0.4	7.1	Fasted four days, convulsions recovered
16	4.8	4,125	9.00	0.8	16.6	Fasted two days, convulsions recovered
16	4.2	2,250	4.25	0.5	11.9	Fasted four days, convulsions recovered
17	4.5	2,700	8.00	0.3	6.6	Fasted two days, convulsions recovered
17	3.8	2,600	6.00	0.3	7.9	Fasted four days, convulsions, recovered
18	6.1	1,800	3.50	0.5	8.2	Fasted two days, convulsions, recovered
18	6.0	2,400	4.00	0.4	6.6	Fasted four days, convulsions, recovered
19	5.9	3,600	5.16	0.6	10.1	Convulsions, recovered
19	5.7	3,300	5.00	0.7	12.2	Water abstinence four days, no different from first experiment, died
20	3.3	1,200	3.00	0.5	15.1	Water abstinence four days, died
21	5.2	3,300	6.00	0.7	18.4	Forced intake of 1,500 c c water each day for two days before experiment, convulsions recovered
22	5.0	3,750	7.00	0.8	16.0	Intake previously forced as in above experiment convulsions recovered

attempts were made to produce water intoxication in some of Mann's dogs with Eck's fistula. The symptoms of poisoning developed in all respects as in normal animals and no difference was observed in the facility with which the intoxication developed.

*The Effect of Ligation of Ureters*—All attempts to produce water intoxication in dogs with ligated ureters failed, probably because of excessive vomiting. In order to prevent vomiting in one of these dogs, a tube was fastened permanently into the duodenum and through this water in large quantities was introduced. Diarrhea resulted, but no manifestations of water intoxication. Similar results were obtained on administering water to a normal dog through a duodenal fistula.

*The Effect of Water Administered by Rectum* <sup>21</sup>—Water was given to dogs by rectum in large quantities, and although the administration was continued at times until water was actually vomited from the mouth, in no instance did water intoxication develop. Warm water

more than enough water to compensate for the rapid loss of fluid is necessary. Not the fluid ingested, but the amount absorbed and assimilated is in all probability responsible for the toxicity.

In searching for an explanation of the development of the foregoing symptoms, the effect of the following procedures and conditions has been investigated since it was thought that they might possibly be concerned, etiologically, in the production of convulsions: (1) repeated passage of the stomach tube, (2) gastric distention, (3) absorption of digestive products and of toxins from the gastro-intestinal tract, (4) the rôle of the liver, (5) ligation of ureters, (6) administration by rectum, (7) intravenous injection and hemolysis, (8) hydremia, (9) edema of brain and increased intracranial pressure, and (10) effect of administration of sodium chlorid.

*Repeated Passage of the Stomach Tube*—Control experiments involving the passage of the tube twenty times, at half hourly intervals, were carried out on dogs. No untoward effects were noted.

*Gastric Distension*—The symptoms were believed to be due, perhaps, to gastric distension, and an attempt was made to prove this by ascertaining the amount of water in the stomach by means of the stomach tube. In dogs, cats, rabbits and guinea-pigs, attempts were made to withdraw fluid from the stomach immediately before, or after, convulsions. In most instances, the amounts withdrawn appeared to be entirely too small to have resulted in marked distention. In some instances, convulsions developed during attempts to vomit, but in others, onset was delayed until long after the vomiting attack. In many instances, in animals dying during convulsions, immediate necropsy showed but little fluid in the stomach.

If distension were the cause of the convulsions they should follow the administration of equivalent quantities of 0.8 per cent sodium chlorid solution. But sodium chlorid solution administered to rabbits and to dogs in double these amounts failed to produce convulsions or any of the significant manifestations of water intoxication. I believe that sufficient evidence has been accumulated through such controls to justify the opinion that gastric distention is not the important factor in the production of water intoxication. However, since this intoxication has developed only in animals to which water was administered by mouth, the factor of distention cannot yet be entirely dismissed from consideration.

*Absorption of Digestive Products and of Enzymes from the Gastro-Intestinal Tract*<sup>21</sup>—In order to determine the part played by too rapid

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<sup>21</sup> These experiments were carried out at the suggestion of Dr. F. C. Mann, and the operations involved were performed by Dr. Mann or members of his staff.

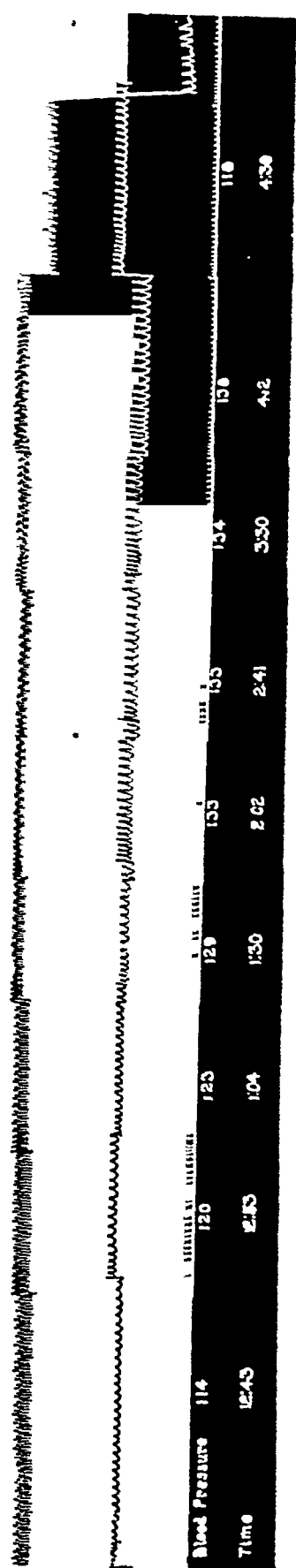
Nov 16 1921

Dog Water Intoxication

Weight 122 Kg



7



Blood Pressure	114	120	123	125	133	134	135	136	118
Time	12:43	12:53	1:04	1:30	2:02	2:41	3:30	4:42	4:50

Record obtained from a case of water intoxication, showing the respiration, blood pressure and intracranial pressure (upper curve)

resulted in relaxation of the sphincter, while cold water occasioned discomfort to the animals and hence its administration was discontinued. Thus, one dog which had previously exhibited convulsions after receiving 3,500 cc of water, when administered by mouth, was subsequently given 6 liters of water at 35 C by rectum during the course of six hours. No symptoms of water intoxication developed. The reason for these results is not clear and further studies along these lines are necessary.

*Intravenous Injection of Water and the Development of Hemolysis*—Distilled water was slowly administered intravenously to two rabbits. The first rabbit died within ten minutes after receiving 25 cc and the second died within one hour and ten minutes after receiving 95 cc. In both instances, marked hemolysis resulted, but in neither case did water intoxication develop. A dog weighing 72 kg was given intravenously 1,275 cc of tap water during a period of two hours and fifteen minutes. Marked salivation, retching, and polyuria resulted. The blood showed hemolysis and the urine was tinged with hemoglobin but water intoxication did not develop.

*Hydremia*—The rôle of hydremia was studied in the previous experiments of Larson, Weir and Rowntree, which showed that water intoxication developed in certain animals subsequent to using the extract of the posterior lobe of the pituitary gland without demonstrable dilution of the blood and without demonstrable increase of the plasma or blood volume. Further studies along these lines are contemplated.

*Edema of the Brain and Increased Intracerebral Pressure*—The marked cerebral disturbances, convulsions, stupor and coma led us to suspect an increase in intracerebral pressure. This was strengthened by the pathologic findings in some animals. The work of Weed and McKibben,<sup>22</sup> of Cushing and Foley,<sup>23</sup> of Foley and Putman,<sup>24</sup> and of Sachs and Belcher<sup>25</sup> on the changes of cerebral pressure, following the administration of hypotonic and hypertonic sodium chlorid solution intravenously, also suggested this possibility. It seemed desirable, therefore, to determine by actual measurement whether or not increased intra-

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22 Weed, L. H., and McKibben, P. S. Pressure Changes in the Cerebrospinal Fluid Following Intravenous Injection of Solutions of Various Concentrations, *Am J Physiol* **48** 512-530, 1919. Weed, L. H., and McKibben, P. S. Experimental Alteration of Brain Bulk, *Am J Physiol* **48** 531-558, 1919.

23 Cushing, H., and Foley, F. E. B. Alterations of Intracranial Tension by Salt Solutions in the Alimentary Canal, *Proc Soc Exper Biol & Med* **17** 217-218, 1920.

24 Foley, F. E., and Putnam, T. J. Effect of Salt Injection on Cerebrospinal Fluid Pressure and Brain Volume, *Am J Physiol* **53** 464-476, 1920.

25 Sachs, E., and Belcher, G. W. The Use of Saturated Salt Solution Intravenously During Intracranial Operations, Preliminary Report, *J A M A* **75** 667-668 (Sept 4) 1920.

0.8 per cent sodium chlorid solution, even when the injections of salt solution were made in the early stages of true water intoxication

Hypertonic sodium chlorid solution was administered to a group of dogs in various stages of water intoxication. In some instances the dogs in stupor, coma or convulsions showed striking improvement within from ten to fifteen minutes after the administration of the sodium chlorid solution, in fact, in many instances, the animals appeared to be practically normal within from one-half to one hour. The induction of water intoxication by the continued use of water becomes a matter of extreme difficulty after a previous administration of 10 per cent salt

TABLE 10—EFFECT OF THE ADMINISTRATION OF SODIUM CHLORID SOLUTION ON WATER INTOXICATION

Dog	Weight, Kg	Water by Mouth, Cc	Time, Hours	Gain in Weight, Kg	Increase, per Cent	Remarks
11	6.0	2,350	4.0	0.9	15.0	1,450 cc of 0.8 per cent sodium chlorid solution intravenously, no convulsions
23	5.1	2,050	5.0	0.5	9.8	55 cc 10 per cent sodium chlorid solution intravenously, no convulsions
23	5.0	3,750	8.0	0.6	12.0	50 cc 10 per cent sodium chlorid solution intravenously, no convulsions
24	4.8	2,250	5.0	0.6	12.5	50 cc 10 per cent sodium chlorid solution intravenously, no convulsions
24	4.6	3,375	8.25	0.5	10.8	50 cc 10 per cent sodium chlorid solution intravenously, no convulsions
25	8.7	3,650	4.0	0.0	6.9	Convulsions followed by 90 cc 10 per cent sodium chlorid solution intravenously, immediate recovery, paralysis of hind legs developed later
26	5.6	3,600 1,500	6.0 2.0	0.5	9.1	Convulsions, twitching, 65 cc 10 per cent sodium chlorid solution intravenously, immediate improvement, paralysis of hind legs developed later
27*	4.7	2,000	3.5	0.6	12.7	Convulsions, followed by 70 cc 10 per cent sodium chlorid solution intravenously, walking about fifteen minutes later, apparently normal in about one and one-half hours
29*	10.8	6,100	5.5	0.8	7.4	Convulsions, 80 cc 10 per cent sodium chlorid solution intravenously, walked within ten minutes, apparently normal one and one-fourth hours later

\* The administration of 4,500 cc and of 10,450 cc of sodium chlorid solution, respectively, to these two dogs failed to elicit any symptoms of water intoxication

solution. It is, therefore, established that hypertonic sodium chlorid solution is effective in preventing or overcoming water intoxication (Table 10)

Excessive accumulation of water may occur as intercellular or intracellular edema. Water may accumulate in the body as an intercellular edema of the dependent parts, or as anasarca with free fluid in the large cavities of the body, without toxicity manifesting itself. In healthy animals increased intracerebral pressure and at times cerebral edema may arise as a result of excessive water ingestion, and is perhaps responsible for most of the phenomena herein described. Whether or not the edema of liver, kidney, and intestinal wall is of any pathologic significance has not been determined as yet. The possibility still exists

cranial pressure accompanied the development of water intoxication. Through the assistance of Dr Meek of the University of Wisconsin, the intracranial pressure of a dog with water intoxication was determined by utilizing the cannula devised by Lowenhart. A tracing from our one flawless experiment demonstrates that an increase in intracerebral pressure can result. Table 9 contains the details of this experiment. These findings are in keeping with those of Weed and McKibben, who demonstrated swelling of the brain through openings in the skull following intravenous injection of hypotonic solution (water), and of Ebaugh and Stevenson,<sup>26</sup> who made measurements of the intracranial pressure changes in a patient with epilepsy. On administering 4 or 5 liters of tap water by mouth for a period of one and one-fourth hours, an increase in intracranial pressure corresponding to 20 mm of water was registered. In one instance Ebaugh and Stevenson administered

TABLE 9—PROTOCOL ON DOG 101, 12.2 POUNDS IN WEIGHT

9 30 a m	Pulse 84, temperature 97.6 F, respiration 26, ether by tracheal tube started, dog voided 20 c.c. of urine, tambour inserted inside of skull, cannulas inserted into femoral veins, apparatus adjusted.
12 45 p m	Pulse 132, temperature 98.8 F, respiration 42, water administered * and tracings started.
12 45 to 3 50 p m	Water in quantities of 200 c.c. introduced every fifteen to thirty minutes, total amount introduced 2,500 c.c., abdomen considerably distended.
4 18 p m	Stomach drained of 1,525 c.c., pulse had varied from 120 to 132 throughout this period.
4 25 p m	400 c.c. of water administered, pulse 120.
4 30 p m	Animal killed, tambour calibrated, total water intake 3,200 c.c., drained from stomach 1,525 c.c., urine in bladder 100 c.c., drained from stomach and intestines 400 c.c., blood lost 170 c.c., calculated water retention about 1 liter.

\* All distilled water administered at temperature between 38 and 40 C.

as much as 8 liters during the course of six hours. The patient complained of fulness, frequency of urination, fulness in the head, tinnitus and headaches, and felt as though an attack were impending.

*Effect of Administration of Sodium Chloride*<sup>27</sup>—It would appear reasonable to consider a disturbance in osmotic relationships and in salt water equilibrium of the brain and nervous system as important features in water intoxication, especially in relation to the nervous manifestations. At any rate, recognition of the increased intracerebral pressure led to experiments involving the use of hypertonic salt solution in an attempt to prevent or overcome convulsions. In early experiments it had already been determined that water intoxication could not be produced through the intravenous administration of large quantities of

26 Ebaugh, F. G., and Stevenson, G. S. The Measurements of Intracranial Pressure Changes in an Epileptic and Its Experimental Variations, *Bull. Johns Hopkins Hosp.* **31**: 440-447, 1920.

27 Hypertonic sugar solution (50 per cent) is also effective, but acts more slowly.

# THE BENZOATE TEST FOR RENAL FUNCTION II \*

F B KINGSBURY, PH D

MINNEAPOLIS

The use of ingested sodium benzoate as a test for renal function was first described by Swanson and me, in a preliminary report before the Federation of American Societies for Experimental Biology, in December, 1920. The full report was published in August, 1921<sup>1</sup>. In June, 1921, Snapper<sup>2</sup> published a report of work along similar lines. He found that after ingesting 5 gm of sodium benzoate, the normal person on a porridge diet eliminated about 75 per cent of it in the form of hippuric acid in the course of six hours. Lewis<sup>3</sup> had previously found a much more rapid elimination of hippuric acid under similar conditions, and this was verified by Kingsbury and Swanson. For this reason, it is believed that Snapper did not obtain all the hippuric acid eliminated in the test specimens of urine, and that these low results were due to the failure of his analytic method. However, Snapper's findings that the rate of hippuric acid elimination after the ingestion of sodium benzoate in 5 gm doses was markedly less in persons suffering from nephritis than in normal individuals, but was little if any less in pneumonia patients and those having complete obstruction of the common bile duct and biliary fistula, are in general accord with the results of Kingsbury and Swanson.

Early results with the benzoate test gave evidence that it was sensitive and would probably indicate early disturbances of renal function. The findings given in this paper confirm this view. Sufficient data had already been obtained to show that, in well marked nephritis, the benzoate tests were always low, but such results were of little value to the clinician who already had made a thoroughly satisfactory diagnosis without the aid of the test. In borderline cases of possible disturbances of renal function, the benzoate test has proved to be of value, and it is mainly to its application in this type of cases that the later discussion will be devoted.

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\* From the biochemical laboratory of the University of Minnesota Medical School.

\* A preliminary report was made before the Society of Biological Chemists, Inc., in Toronto, Canada, December, 1922.

1 Kingsbury, F B, and Swanson, W W. The Synthesis and Elimination of Hippuric Acid in Nephritis. A New Renal Function Test, *Proc Am Soc of Biol Chemists* **15** 4 (Dec) 1920, *Arch Int Med* **28**:220 (Aug) 1921.

2 Snapper, I. The Elimination of Hippuric Acid, *Nederl Tijdschr v Geneesk* **1** 3044 (June) 1921.

3 Lewis, H B. The Synthesis and Rate of Elimination of Hippuric Acid After Benzoate Ingestion in Man, *J Biol Chem* **18** 225 (July) 1914.



that edema of the intestinal wall may so damage the specific absorption of the intestinal epithelium that toxic products from the canal may enter directly into the blood stream. It is peculiar that to date this intoxication could be produced only by water administered by stomach tube. This fact renders difficult an exact explanation of the mechanism involved.

#### CONCLUSIONS

1 In man and animals (dog, cat, rabbit and guinea-pig) water ingested in excess of the ability of the organism to excrete it leads to water intoxication.

2 Water intoxication is manifested by restlessness, asthenia, polyuria, frequency of urination, diarrhea, salivation, nausea, retching, vomiting, muscle tremor and twitching, ataxia, tonic and clonic convulsions, frothing at the mouth, helplessness, stupor and coma.

3 The convulsions are general in character, of extreme violence and in the main resemble those of strychnin poisoning. They may recur at intervals of a few minutes.

4 Water intoxication terminates in death unless the excessive intake is discontinued.

5 Water intoxication may be acute, ending in death in from four to twelve hours, or subacute, lasting for some days. Subacute intoxication results from smaller amounts of water continued over a longer period of time.

6 Water intoxication is accompanied by, and is probably due, in part at least, to increased intracerebral pressure, this in turn is probably a manifestation of disturbance in the salt water equilibrium of the central nervous system.

7 Water intoxication can be prevented, alleviated or cured by the timely intravenous administration of hypertonic sodium chlorid solution.

concentration of hippuric acid was low, required the use of 50 c c for analysis. The case with benzoate test specimens is different, for the concentrations of hippuric acid are usually so much greater that 25 c c are sufficient for analysis. In both the normal and pathologic series of tests, the method of making the test was uniformly as described. The sodium ethylate used in titrating the resulting benzoic acid is standardized against pure benzoic acid in chloroform solution, with phenolphthalein as indicator. The calculations are simple. 24 gm of sodium benzoate is taken as equivalent to 2 gm of benzoic acid. The hippuric acid resulting from the ingestion of benzoate is determined as benzoic acid, and the amount of this found in a test specimen of urine divided by 2 and multiplied by 100 gives the percentage of elimination.

#### EXPERIMENTAL DATA

It was necessary to make a larger series of determinations on normal subjects since the series already reported was rather small and contained no two-hour elimination values. The results are shown in Table 1. Medical students were the subjects mainly, but a few values obtained from patients known to be free from any renal disturbances are included. Several of the freshman medical students made tests on themselves, including the necessary analyses, as part of their regular work in physiologic chemistry. Their figures, checked by analyses made in this laboratory, are included in the series. In this connection, it is pointed out that the analytic work involved in making these tests is as easily and successfully handled by students as any other method of analysis required in their course. It will be noted that the average two-hour excretion of hippuric acid under the conditions of the test for forty-four normal individuals is 82 per cent of the ingested dose of sodium benzoate and the third-hour excretion is 16 per cent. The limits for the two-hour test are from 70 to 91 per cent, and for the third hour, from 32 to 8 per cent. The average total three-hour output is 98 per cent, which agrees closely with the value, 97 per cent, found by Swanson and myself, under conditions which were not so closely prescribed with respect to the time when the test was made, and the amount of water ingested. It is also to be noted that the previous series was made on a smaller number of normal individuals, and that the hippuric acid was determined by the method of Folin and Flanders<sup>5</sup>.

In Table 1 are also shown the two and one hour volumes of urine in the normal test specimens. In about 50 per cent of the normal two-hour tests, a marked diuresis is noticed. The actual concentration

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<sup>5</sup> Folin, O., and Flanders, F. F. A New Method for the Determination of Hippuric Acid in Urine, *J Biol Chem* **11** 257 (April) 1912

As originally described, the test determines the three-hour output of hippuric acid after the ingestion of 2.4 gm of sodium benzoate. With the exception of ruling out fruit from the diet during the time of the test, no conditions as to the intake of food or water during the test were prescribed. In the present work, such conditions were specified, and all the results given in this paper were obtained in benzoate tests carefully regulated and therefore uniform. The hourly elimination of hippuric acid during the three hours of the test was studied with persons in normal health and those presenting pathologic conditions, but it was found that nothing was gained in making the test in this manner. If the test was made in a two-hour period followed by a one-hour period, more information as to the ability of the kidney to excrete hippuric acid under the conditions of the test could be obtained, for in some pathologic cases in which a normal or nearly normal result was obtained for three hours, the two-hour elimination was definitely below normal, while the third hour elimination was sufficient to bring the total for three hours up to a normal value.

#### METHODS

Since many fruits contain benzoic acid or substances which may be converted into it in the body, they must be omitted from the diet before and during the period of the test. The patient is denied fruit at the evening meal on the day before the test. On rising the patient voids urine, and immediately thereafter drinks a solution of 2.4 gm of sodium benzoate in about 100 cc of water. The container is rinsed with about 200 cc, and this is also drunk. At the end of one hour, 200 cc of water is drunk, making a total water intake of 500 cc, and at the end of two hours the first sample of urine is collected. The second specimen of urine, representing the third hour of the test, is collected one hour later. Both specimens of urine are preserved, unless they can be analyzed immediately. Preservation is effected by adding about 10 drops of a 10 per cent solution of thymol in chloroform to each specimen, 15 cc of 2 per cent nitric acid to the two-hour specimen, and 7 cc of the same solution to the one-hour specimen. The total volume of each specimen must be measured and an aliquot part taken for analysis. I have used the method previously described<sup>4</sup> for all the tests reported in this paper, with the slight modification of using half quantities of urine and all other materials necessary, keeping the time element for the various operations the same. The method as originally described was designed for use with any sample of urine, and, to be adequate for twenty-four hour normal urines in which the

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<sup>4</sup> Kingsbury, F. B., and Swanson, W. W. A Rapid Method for the Determination of Hippuric Acid in Urine, *J. Biol. Chem.* **48** 13 (Sept.) 1921.

benzoate test, I am not prepared to modify the view expressed in the first paper on this subject that such experiments are practically unnecessary when the test is made in the way described, because of the great variability in the dose of sodium benzoate per kilogram of body weight and the difficulty in collecting test samples of urine with an accuracy which would warrant it. In the direction of increasing the accuracy of this test, all these factors must be considered.

As to what constitutes a normal test, I think that a two-hour test with elimination of less than 70 per cent and a three-hour test with elimination less than 90 per cent should be regarded as low, and the tests recorded in this paper have been judged on this basis. In cases,

TABLE 2—*Normal Benzoate Tests Corrected*

Subject	Total 3 Hour Benzoate Test, per Cent	Three Hour Normal Morning Urine Hippuric Acid as Benzoic Acid, Gm	Corrected Benzoate Test, per Cent
6	99	0.06	96
7	100	0.14	93
8	94	0.08	90
9	102	0.12	96
10	98	0.10	93
12	98	0.15	90
13	97	0.15	90
14	96	0.23	85
15	101	0.10	96
16	93	0.10	88
17	98	0.12	92
18	99	0.16	91
19	96	0.06	93
21	103	0.12	97
22	91	0.03	90
23	100	0.15	93
28	105	0.09	101
31	106	0.11	100
32	95	0.22	84
35	104	0.08	100
38	99	0.09	95

a few of which have occurred, in which the elimination in a two-hour test is low but is followed by a third hour elimination which is sufficiently high to make the total for three hours of 90 per cent or better, unless there is good evidence of marked delay in the passage of materials from the stomach into the intestines which could account for this by delaying the absorption of the sodium benzoate, it seems necessary to attribute this result to a slightly lowered renal function. In normal tests in which by mistake the urine is collected in a one-hour period followed by a two-hour period, the results to be expected are a nearly even partition between the two periods of the total excretion of hippuric acid for the three hours.

Two experiments carried out on a normal subject are of interest in connection with the test. The first experiment shows the effect of drinking large quantities of water, and the second, the effect of the ingestion of a large amount of cranberries. The results of the first

of hippuric acid in each two-hour specimen has been calculated (not shown in the table), and varies from 0.32 per cent to 3.14 per cent

It will also be seen that the dose of sodium benzoate per kilogram of body weight varied from 26.7 mg in Subject 14, who weighed 90 kg, to 50 mg in Subject 11, who weighed 48 kg

TABLE 1—Normal Benzoate Tests

Subject	Sex*	Weight, kg	Hippuric Acid Excreted			Urine 2 Hours, Cc	Doses of Sodium Benzoate per kg. of Body Weight, Mg
			2 Hours per Cent	3 Hours, per Cent	2 Hours, Gm		
1	♂	68	91	102	2.67	123	35.3
2	♂	73	89	98	2.36	289	32.9
3	♂	68	88	96	2.38		35.3
4	♂	66	92	102	2.70		36.4
5	♂	65	86	96	2.52		36.9
6	♂	61	82	99	2.41	595	39.4
7	♂	70	87	100	2.55	296	34.3
8	♂	67	83	94	2.44	190	35.7
9	♂	82	86	102	2.52	340	29.3
10	♂	61	87	98	2.55	370	39.3
11	♂	48	75	100	2.20	670	50.0
12	♂	60	76	98	2.23	109	40.0
13	♂	51	78	97	2.29	360	47.0
14	♂	90	87	96	2.55	395	26.7
15	♂	70	77	101	2.20	355	34.3
16	♂	70	81	93	2.38	293	34.3
17	♂	61	78	98	2.29	153	39.3
18	♂	71	88	99	2.58	100	33.6
19	♂	64	80	96	2.35	144	37.5
20	♂	77	87	98	2.55	146	31.2
21	♂	70	88	103	2.58	504	34.3
22	♂	54	73	91	2.15		44.4
23	♂	61	78	100	2.29	95	39.3
24	♂	61	81	95	2.38	480	39.3
25	♂	73	88	101	2.58	138	32.9
26	♂	73	83	100	2.44	152	32.9
27	♂	66	73	89	2.14	118	36.4
28	♂	77	91	105	2.65	271	31.2
29	♂	70	92	102	2.70	325	34.3
30	♂	65	81	99	2.38	415	36.9
31	♂	88	84	106	2.46	248	27.3
32	♂	70	74	95	2.17	113	34.3
33	♂	73	76	93	2.23	71	32.9
34	♂		85	99	2.49	390	
35	♂	71	81	104	2.38	650	33.6
36	♂	64	84	98	2.46	126	37.5
37	♂		87	95	2.55	615	
38	♂	73	84	99	2.46	650	32.9
39	♂		81	99	2.38	300	
40	♂		71	89	2.08	122	
41	♂		90	102	2.65	840	
42	♂		83	105	2.44	465	
43	♂		70	100	2.05	498	
44	♂		72	104	2.11	480	

\* In this column, ♂ indicates male, ♀ female

In twenty-one of the normal tests, the three-hour output of hippuric acid when no benzoate had been ingested was also determined. This was done for the first three hours of the morning on one day. On the following day, benzoate tests were made, and the amount of hippuric acid which was so found, independent of the sodium benzoate ingested, was in each case subtracted from the values given by the tests. These data are shown in Table 2. Although these results indicate that control experiments made in this way might increase the accuracy of the

exception of the benzoate tests, were obtained from the hospital. In Table 5 are shown the summarized data from thirty-nine patients. The fact that elimination in the benzoate test is always low in nephritis has already been shown,<sup>1</sup> and is confirmed by the results presented in this paper. When the diagnosis of this condition is clear cut, there seems to be little need of making benzoate tests. The value of this test lies in showing the degree of impairment of renal function early in glomerulonephritis, nephrosis, pyelonephritis and arteriosclerosis of the kidney. It is also useful in determining the degree of improvement in function following the acute renal injury in toxemia of pregnancy. The details of cases will be limited to numbers 41, 42, 43, 48, 54, 56, 58, 60, 67 and 68. The diagnoses of these cases were made by Dr. George E. Fahr of the department of medicine, who kindly furnished data of certain other tests of renal function which he had made. These are the water excretion test of Volhard,<sup>6</sup> the determination of the constant of Austin, Stillman and Van Slyke,<sup>7</sup> MacLean's urea concentration test<sup>8</sup> and the phenolsulphonephthalein test of Rowntree and Geraghty.<sup>9</sup>

#### REPORT OF CASES

**CASE 41—*Diagnosis: Toxemia of pregnancy*** On entrance to the hospital, the patient showed edema of the face and lower extremities, and a blood pressure, 190 systolic, and 110 diastolic. Examination of the urine revealed granular and hyaline casts and a relatively large amount of albumin. Blood urea nitrogen and creatinin at this time were 23 mg. and 3 mg. respectively, in 100 c.c. of blood. Four phenolsulphonephthalein tests resulted in 85, 69, 65 and 65 per cent elimination in two hours. About one month after entrance to the hospital, at the beginning of labor, the blood pressure was 160 systolic, and 125 diastolic. At about this time, there was a considerable amount of albumin in the urine. A benzoate test six days before parturition resulted in 50 per cent elimination in two hours, with a total for three hours of 69 per cent, definitely low. At the time of the patient's discharge from the hospital, the blood pressure was normal as was also the urea nitrogen of the blood. Urinary findings were normal.

**CASE 42—*Diagnosis: Subchronic glomerulonephritis*** The blood pressure was 140 systolic, and 82 diastolic. Examinations of the urine revealed albumin and casts constantly present. Two phenolsulphonephthalein tests were normal, elimination being 66 and 63 per cent in two hours. The blood showed a retention of urea. The results in the benzoate test on three occasions were constantly low. The result in MacLean's urea concentration test was 0.9 per cent. The

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6 Volhard, F., and Fahr, T. *Die Brightsche Nierenkrankheit*, Berlin, 1914, pp. 121, 126.

7 Austin, J. H., Stillman, E., and Van Slyke, D. D. Factors Governing the Excretion Rate of Urea, *J. Biol. Chem.* **46**: 91 (March) 1921.

8 MacLean, H., and de Wesselow, O. L. V. On the Testing of Renal Efficiency, With Observations on the "Urea Coefficient," *Brit. J. Exper. Pathol.* **1**: 53 (Feb.) 1920.

9 Rowntree, L. G., and Geraghty, T. L. An Experimental and Clinical Study of the Functional Activity of the Kidneys by Means of Phenolsulphonephthalein, *J. Pharmacol. & Exper. Therap.* **1**: 579, 1910.

experiment are shown in Table 3. It will be seen that by drinking 1,850 c c of water during the first two hours of the test, the excretion of hippuric acid can be raised from a normal average value of about 80 to 85 per cent, with a water intake of about 500 c c, to 100 per cent, the value for a three-hour test.

The effect of eating 240 gm of cranberries with 100 gm of sucrose, for the evening meal, on the output of hippuric acid for the next few hours is shown in Table 4. As will be seen, there is little increase in the output of hippuric acid over the normal for the first three hours. The bulk of hippuric acid is formed and excreted during the next eleven hours, and the rate of excretion has become nearly normal again.

TABLE 3—*The Effect on the Benzoate Test of Drinking a Large Quantity of Water*

Time	Water Ingested, C c	Urine C c	Excretion per Cent	Remarks
11 17 a m	600			2.4 gm sodium benzoate ingested
11 47 a m	700	302	25	
12 17 a m	250	406	64	
12 47 a m	250	387	89	
1 17 p m	250	298	100	

TABLE 4—*Effect of Eating Cranberries in the Normal Subject*

Time	Urine Voided, C c	Hippuric Acid Excreted, Gm	Remarks
6 00 p m			240 gm of cranberries boiled with water, and 100 gm of sucrose ingested
7 00 p m	90	0.170	
8 00 p m	363	0.150	
9 00 p m	31	0.109	
11 50 p m	178	0.642	
8 00 a m	358	1.773	
11 00 a m	779	0.358	

within fourteen hours. Under normal conditions, cranberries, which are relatively rich in benzoic acid, could be eaten in large quantities at the evening meal without appreciably affecting the results of the benzoate tests made the following day on normal subjects. This would probably apply equally well to the ingestion of fruits. With subjects suffering from pathologic conditions, it could not be assumed that the ingestion of large amounts of cranberries or fruit at the evening meal preceding the test would be without effect on the test itself. For this reason, the procedure of ruling out fruit as outlined above was strictly adhered to.

#### TESTS ON HOSPITAL PATIENTS

These were carried out in the University Hospital, with the cooperation of the department of medicine. All laboratory data, with the

50	♂♂	53	87	93 13 23 29 17 18 39 88 95	6 8	47 87	49 26	108 325		Normal, no disease Chronic nephritis	- +	
51			16 18 11 39 88							Lobar pneumonia Normal as far as kidneys are concerned	- -	Discharged Discharged
52	♂♀	27 32	57 35	74 50	58 24	50 21 36	29 25 23	80 89 80		Pyelonephritis, bronchopneumonia	+	Died
53	♂	32	86	97						Normal as far as kidneys are concerned	-	
54	♀	21								Hypertension	-	Delivered, 1/18/22, discharged
55	♀	36	56 66 54	80 86 75	40 38 63 46	19 16 16 12 18	20 20 22 20	91 90		Goiter, normal as far as kidneys are concerned	-	Discharged
56	♀	16	72	94				64		Subchronic glomerulonephritis	+	Discharged
57	♀	27	23	36	5	51	60	100	138		+	Discharged
58	♀	21	19	77	67	21	21	80	175		+	Discharged
59	♂	21	49		43 54	26 22	30 28		120			
60	♀	52	70 57 12	89 84 31	63 54 36	12 12	19	103	190	Hypertension, arteriosclerotic kidney	-	Discharged
61	♀	17	57	71	54	25	23	80		Chronic nephritis, hydronephrosis of right kidney	+	Died
62	♂	24	57 5	14	7	23 49 51 63	20 40 50 60	112 118		Left kidney removed clinical evidence of other kidney being involved	+	Alkaline reserve reduced, benzate test after nephrectomy
63	♂	26	76	87	46					Tuberculosis of left kidney, kidney removed, no clinical evidence of other kidney being involved Addison's disease	-	Died 3/13/22
64	♂	36	67	89	42 54	19	17	80		Edema and clinical indications of renal involvement	+	Delivered 3/14/22, benzoate test 2 days previously, discharged
65	♀	24	34	61	20	14	20			Abnormal pregnancy, toxemia of pregnancy	+	Discharged
66	♀	38	61	77	58				190-200	Hypertension		
67			35	61	52	10			145 in bed, 224 when up	Early state of hypertension		
68			70	100	79 83		19					

\* In this column, ♂ indicates male, ♀, female † In 1½ hours ‡ In 6¼ hours



TABLE 5—Summary of Benzoate Tests in Thirty-Nine Patients

Case	Sex*	Age	Benzoate Test		Phenol sul- phone phthal- ein, 2 Hrs, %	Blood (100 C c)			Blood Pressure		Diagnosis	Albu- min	Remarks
			2 Hrs per Cent	3 Hrs per Cent		Urea Nitro- gen, Mg	Creat- inin, Mg	Glu- cose, Mg	Sys- tolic	Das- tolic			
30	♀	50		40 40	28 18	29 13	1.9 1.1	102 90	190	110	Chronic nephritis	—	Discharged, condition unchanged
31	♀	34		82	49	18	2.6	195			Chronic pulmonary tuberculosis	—	Discharged, condition unchanged
32	♀	60		87	15	40	4.0	151	165	100	Hypertension, obesity	—	Discharged, improved
33	♀	36		10		52	5.4	129			Chronic nephritis	—	Discharged
34	♂	62		10		56	4.4	132			Chronic glomerulonephritis	+	Discharged
35	♂	27		22	trace	55	8.0	111	180	112	Chronic glomerulonephritis, car- diac hypertrophy	+	Died 1/22/22
						54	8.5	117					
						45	8.7	135					
						38	5.1	120					
						30	5.4						
36	♂	14		66	95	23	1.8	129	130	70	Chronic nephritis	+	Discharged
37	♂	23		15	0	95	9.1	120			Chronic nephritis	+	Discharged
38	♂	52		37		28	3.2	132	164	120	Acute nephritis, cardiac disease	+	Discharged
39	♂	52		44		34	2.6	81	150	120	Arteriosclerosis, chronic cardiac hypertrophy, auricular fibrillation	+	Died 10/22/21
40	♂	23		74	85	24	3.8	93	176	120	Acute nephritis	+	Discharged, improved
41	♀	24	50	69	69	23	3.0		190	110	Toxemia of pregnancy, ne- brosis	+	
									160	125			
42	♀	28	65	82	66	32	2.7	87	140	82	Subchronic glomerulonephritis	+	Discharged
			50	71	63		1.9						
43	♀	26	59	85	55	25	2.5	82			Toxemia of pregnancy, nephrosis	—	Discharged, improved
			64	87	55	23	2.3						
			75	95		21	2.9						
			76	93		11	1.7						
						10							
						42	4.6	100					
44	♂	50	19	30	15	80	7.5	140	148	96	Chronic glomerulonephritis	+	Discharged
45	♂	67	44	61			2.1	78			Chronic myocarditis, emphysema	+	Discharged
46	♀	50	57	74	56	20					Chronic nephritis, hypertension	—	Discharged, water excretory func- tion impaired (Volhard's test)
47	♂	27	16	22	49	80					Chronic nephritis	+	Discharged
48†	♂	72	101	101	82	Normal	Normal	Normal			Duodenal ulcer	+	Discharged
49	♂	51	13	24	15	103	11.0	80			Hydronephrosis, pyelonephritis	+	Phenolsulphonethalalin and benzoate tests on left kidney alone, died
	♂		44	62	24	91	9.0	80			carcinoma of rectum	+	
						46	3.0	137					
						67	8.0						
						126							

CASE 58—*Diagnosis Subchronic glomerulonephritis* Elimination in MacLean's test was 0.65 per cent, definitely low, phenolsulphonephthalein output on two occasions was 5 and 6 per cent in two hours, elimination by benzoate tests 23 per cent in two hours, with a total for three hours of 36 per cent, the constant of Austin, Stillman and Van Slyke was 1.1 and 0.7 on two occasions, definitely low. There was a considerable retention of urea in the blood.

CASE 60—*Diagnosis Hypertension with arteriosclerotic kidneys* There was a variation in the specific gravity of the urine of 1.002 and 1.016, with day and night volumes of 1,209 and 1,600 cc, respectively. The systolic blood pressure was from 180 to 215 during rest in bed. Elimination in MacLean's test was 15 per cent, definitely low, the phenolsulphonephthalein output was 63 and 54 per cent on two occasions. A urea nitrogen test of the blood showed no retention. The constant of Austin, Stillman and Van Slyke was 4 and 2.5 on two occasions, the first value being on the borderline of normality and the second low. Elimination by the benzoate test was normal on the first occasion, and slightly, but definitely, low on the second, agreeing closely with the findings by the constant of Austin, Stillman and Van Slyke.

CASE 67—*Diagnosis Hypertension* The constant of Austin, Stillman and Van Slyke was 5, which is within normal range. The result with Volhard's water excretion test was low. MacLean's test, 18, was nearly normal, but results with the benzoate test were decidedly low, 35 per cent for two hours, with a total of 60 per cent for three hours. Systolic blood pressure ranged from about 190 to 200.

CASE 68—This patient had shown a high blood pressure for the preceding four years, with a present systolic pressure of 224 when up and about, and 148 when in bed. Albumin and casts were found during the first pregnancy. Recently, a few casts and a trace of albumin had been noted. The eye-grounds indicated hypertension. Urea nitrogen and creatinin were at a normal level in the blood. The constant of Austin, Stillman and Van Slyke was normal (7.8), results in the benzoate test, Volhard's, MacLean's and the phenolsulphonephthalein test were all normal. This case was diagnosed as essential hypertension. It is to be noted that none of the renal function tests indicate any reduction of kidney sufficiency.

#### SUMMARY AND CONCLUSIONS

1 The benzoate test indicates the impairment of renal function early. There is a fairly close agreement in this respect with the water excretion test of Volhard, the urea concentration test of MacLean, and the constant of Austin, Stillman and Van Slyke, in the few cases in which the comparison was possible.

2 The benzoate test indicates renal insufficiency earlier than does a test of the urea content of the blood. Low results in benzoate tests have been noted in cases showing at the same time a normal concentration of urea in the blood. Normal indications in benzoate tests have not been obtained on patients whose blood showed at the same time a retention of urea. For this reason, it seems unnecessary to make urea determinations in the blood until benzoate tests have first been made and have shown a definite renal insufficiency.

3 The results of this paper confirm and extend those of Swanson and myself. Additional data have been presented on the test with normal individuals, by which to judge the results obtained with patients.

normal kidney under the conditions of this test effects a concentration of urea of 2 per cent or more. The constant of Austin Stillman and Van Slyke was also low, 18, the normal constant being 75 plus or minus 3. The condition of the patient at the time of discharge from the hospital showed no improvement. The close agreement between the findings by the benzoate test and those of MacLean and Van Slyke and co-workers is to be noted. This is in harmony also with the blood findings. The phenolsulphonephthalein test failed to indicate any renal injury.

CASE 43—This patient on admission to the hospital had a blood pressure of 165 systolic, and 120 diastolic. Examination of the urine revealed many granular and hyaline casts and a large amount of albumin. The blood showed a slight retention of urea. A phenolsulphonephthalein test at this time resulted in an elimination of 36 per cent in two hours. Shortly after parturition, a benzoate test resulted in 64 per cent elimination in two hours with a total for three hours of 87 per cent, slightly, but definitely, low. A phenolsulphonephthalein test four days previously was normal. The blood at this time contained 10 mg of urea nitrogen and 17 mg of creatinin in 100 cc. Urinary findings, except for a very slight trace of albumin, were normal. Subsequently, two benzoate tests were normal, the urinary findings and blood pressure were normal, and the patient was discharged from the hospital. The diagnosis of this case was toxemia of pregnancy. It is to be noted that at the time the blood findings had indicated a return to the normal condition, there was still a slight indication of renal insufficiency by the benzoate test. This was not shown by the phenolsulphonephthalein test.

CASE 48—*Diagnosis Duodenal ulcer*. A lowering of elimination in the benzoate test would perhaps be expected in this case because of the possibility of the duodenal ulcers interfering with the normally rapid absorption of sodium benzoate. The benzoate test specimens, through an error, were collected one and three quarters and six and a quarter hours, respectively, after the ingestion of the 24 gm of sodium benzoate. The values obtained 46 per cent in the first period and 101 per cent for the total period, are low but are probably not due to any impairment of renal function in this particular case.

CASE 54—*Diagnosis Pylonephritis*. On one occasion, high and on another occasion low elimination was shown in a phenolsulphonephthalein test. Results in the benzoate test were low on both occasions. There was a considerable retention of urea nitrogen in the blood, which was lowered somewhat by treatment. The constant of Austin, Stillman and Van Slyke, 28, was definitely low.

CASE 56—A pregnant woman infrequently gave slightly positive reactions in tests for albumin in the urine, and occasionally a hyaline cast was found. The systolic blood pressure was never below 190, even when the patient was resting in bed. On the administration of nitroglycerin, there was a rise in blood pressure. Results in Volhard's water excretion test were definitely low. There was no edema. Elimination in MacLean's test was 1 per cent, a definitely low result. Phenolsulphonephthalein output varied from 40 to 63 per cent in two hours. The constant of Austin, Stillman and Van Slyke was 23, 23, and 28 on three occasions, all definitely low. Elimination in benzoate tests, one made before delivery and two afterward, was, respectively, 56 per cent in two hours, with a total of 86 per cent for three hours, 54 per cent for two hours with a total of 75 per cent for three hours, and 66 per cent for two hours with a total of 86 per cent for three hours, all results being slightly, but definitely, low. Urea and creatinin in the blood taken at the time of labor were in normal amount. Blood pressure findings after parturition showed a definite improvement in the patient's condition and were normal at the time the patient was discharged from the hospital. Data from the university dispensary showed this to be a case of hypertension.

saturated salt solution, then filtered and titrated. The two titration figures obtained were 0.08 c c and 0.12 c c of one-tenth normal sodium ethylate. The blank on 200 c c of the same toluene similarly treated using water instead of urine was 0.10 c c. No free benzoic acid was found, not even a determinable trace, although in the three-hour period the patient excreted 0.362 gm of hippuric acid and in the following twenty-one hour period 1.836 gm of hippuric acid. This is the type of nephritis which presumably is that designated by Morgulis and his co-workers as "parenchymatous," in which they claim that free benzoic acid was excreted.

Our explanation of the main source of error in the work of Morgulis, Pratt and Jahr is that they extracted some of the hippuric acid present, since chloroform, which they used for this purpose instead of toluene, is well known to have a solvent effect on hippuric acid, and the hippuric acid so extracted was titrated and called free benzoic acid. Possibly two other sources of error also crept into their work, for otherwise it is hard to explain the magnitude of the blanks which they mistook for free benzoic acid. The first is that of using acid samples of chloroform. Long experience on the part of one of us has taught that chloroform is a most uncertain substance in this respect unless carefully washed just prior to use, and the second is that of the spontaneous decomposition of hippuric acid with the resultant release of free benzoic acid in specimens of urine not carefully acidified. We used adequate amounts of 2 per cent nitric acid which prevents this accidental hydrolysis, as Raiziss and Dubin have found, and which we have confirmed many times in this laboratory.

## ADDITIONAL OBSERVATIONS

Since this article was prepared, a paper by Morgulis, Pratt and Jahr<sup>10</sup> has appeared containing misleading allusions to the original work of Kingsbury and Swanson and criticisms of some of their conclusions.

These authors, by finding what was apparently free benzoic acid in the urine of patients with parenchymatous nephritis who had been given sodium benzoate by mouth, concluded that some benzoic acid had escaped conjugation with glycine. The claim was made that our "assumption" of the nonoccurrence of free benzoic acid in the urine in such cases was incorrect. We made no such assumption as this but determined the fact (see page 7 of our original paper<sup>1</sup>). This was done in a case of glomerulonephritis, the diagnosis of which was checked by necropsy findings and in a case of nephritis of the arteriosclerotic type which was also checked by necropsy, as well as in two so-called cardiorenal cases. After giving each of these patients the prescribed dose of 24 gm of sodium benzoate, the three-hour urine specimens were analyzed by the Raiziss and Dubin<sup>11</sup> method for free benzoic acid (albumin having previously been removed by our procedure). The titration figures obtained were blanks inherent in the analytic procedure and did not represent any detectable amount of free benzoic acid. For ordinary 100 c c samples of urine such blanks were from 0.05 to 0.10 c c of one-tenth normal sodium ethylate. Using distilled water in place of urine, the same blanks were obtained.

In confirmation of this earlier work, an experiment was quite recently made on a case of glomerulonephritis which was fatal about one week after the benzoate test was made. This patient showed a marked retention of urea nitrogen, and necropsy subsequently proved that the diagnosis was correct. Sodium benzoate, 2.97 gm (18 gm per square meter of body surface) were given to this patient, and the three and the twenty-four hour output of hippuric acid determined. This amounted in three hours to 10 per cent and in twenty-four hours to 60 per cent, in both cases being wholly in the form of hippuric acid as the determinations below show. Large samples, 170 c c and 250 c c, respectively, of the three and the twenty-one hour specimens were analyzed by the method of Raiziss and Dubin after albumin had been removed. Five cubic centimeters of concentrated nitric acid for acidifying the urine specimens and approximately 100 gm of ammonium sulphate were added and four extractions made with 50 c c portions of neutral, washed toluene. The combined 200 c c portions of toluene extract in each case were washed with 100 c c of the Folin-Flanders

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<sup>10</sup> Morgulis, S., Pratt, G. P., and Jahr, H. M. Hippuric Acid Synthesis as a Test for Renal Function, *Arch Int Med* **31** 116 (Jan) 1923.

<sup>11</sup> Raiziss, G. W., and Dubin, H. On the Estimation of Benzoic Acid in the Urine, *J Biol Chem* **20** 125 (Feb) 1915.

factor in producing sources of error. The ideal method would be one in which the end-point is determined by viscosity changes in the blood with a minimum of agitation, since agitation delays the gelation, and in which the blood is kept at or near body temperature from the time of drawing. These ends must be attained without complexity of procedure or apparatus, if the method is to be clinically useful.

During the last few months, one of us, in making studies of the clotting time under various conditions, found that none of the foregoing methods answered our needs fully, owing either to the complexity of the method, or its inaccuracy under varying external conditions, and we therefore sought for a simple yet dependable method that could be applied at any time or place with little difficulty.

The following method, which has now been used in hundreds of determinations, answers these requirements. Its sources of error are quite easily controlled, as we have determined by careful tests. The results, for practical and comparative purposes, are surprisingly accurate.

The method depends on the fact that blood ceases to flow back and forth in a capillary tube at the first sign of clotting. Capillary tubes of from 0.6 to 0.8 mm. inside diameter are drawn from clean glass tubing and cut into about  $1\frac{1}{4}$  inch lengths. The blood is obtained from a stab wound of the finger or ear, the first drop being wiped off. The tube is touched to the second drop, and the blood is allowed to flow in by capillarity, leaving about one fourth inch unfilled. Time is counted from the appearance of the second drop over the wound. Some pressure, provided it is applied at a little distance from the wound, is permissible in getting the drop to form rapidly. After filling, and in order to secure a constant and definite temperature, the tube is placed in one of the creases of the palm and completely covered by closing the hand. This gives a uniform temperature, somewhat below that of the body (about 35 C.), and obviates the necessity of a water bath or chamber of any sort. By simply opening the hand slightly for observation when inverting the tube, one may note the end point without changing the temperature or disturbing the tube. The tube should be gently inverted every thirty seconds, and observation made of the time when the column ceases to move, on being so inverted. Jarring and shaking tend to prolong the clotting time and should therefore be avoided.

The diameter of the tube should be sufficient to allow a rather free flow of the blood when the tube is held upright just after filling. If the tube is too small, the attraction of the glass, a slight drying at the two ends of the blood column and an increase in the viscosity of the blood on cooling slightly all tend to impede the flow, with the result that the real end-point cannot be distinguished.

# A NEW METHOD FOR ACCURATELY DETERMINING THE CLOTTING TIME OF THE BLOOD\*

MORITZ F PETERSEN, M D

AND

C A MILLS, PH D, M D

*Medical Fellow of the National Research Council*

CINCINNATI

The coagulability of the blood is often one of the most important factors with which the clinician must deal. In all cases of bleeding, it is essential to determine whether the cause is a delayed coagulation of the blood or some other factor, such as local infection and injury of blood vessels. This is especially true in purpura, hemophilia, bleeding in the new-born and jaundice, and in preoperative examination of patients. An accurate method of estimating this property of the blood is therefore essential for the proper handling of such cases. For clinical use, the method must be simple and require little apparatus.

Many methods have been advocated to determine the clotting time, their very number indicating that none is quite satisfactory. A complete and comprehensive review of all these methods up to 1907 is found in a paper by Hinman and Sladen<sup>1</sup>. Since that time, a number of modifications of the old methods, and a few new ones have been described. We will consider only the fundamental shortcomings of these methods.

As regards the temperature factor, several investigators have shown the marked effect of the temperature on the clotting time, while Rudolph<sup>2</sup> goes so far as to say that there is one minute difference for each degree of change in temperature between 15 and 20 °C. Many of the methods in use disregard this important factor entirely, while others attempt to control it by means of water-bath devices. With the temperature uncontrolled, the methods lose most of their value even for comparative work, while all water bath devices are either too small to maintain a constant temperature, or are too complicated for widespread clinical use.

In the Brodie and Russell method<sup>3</sup> and its modifications, the factors of evaporation and agitation of the blood are added to the temperature

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\* From the departments of pediatrics and medicine, University of Cincinnati Medical College and Cincinnati General Hospital.

1 Hinman, F, and Sladen, F J. Measurement of the Coagulation Time of the Blood and Its Application, *Bull Johns Hopkins Hosp* **18** 207, 1907.

2 Rudolph, R D. A Clinical Method of Estimating the Coagulation Time of the Blood, *Am J M Sc* **140** 807 1910.

3 Brodie, T G, and Russell, A E. The Determination of the Coagulation Time of Blood, *J Physiol* **21** 403, 1897.

ate lunch at about the same time, i e, 12 m to 12 30 p m The clotting times were taken about three and one half hours later, as shown in Table 3

The method is reliable in giving similar results under like conditions, when the precautions mentioned earlier are observed It does not give the true clotting time of the blood alone, since the method of obtaining the blood allows of an admixture of tissue juices from the wound edges

TABLE 2—*Constancy of Clotting Time*

Time	Clotting Time	
	Hr	Min
7 33 a m	2	50
7 40 a m	2	50
7 50 a m	2	50
7 53 a m	2	50
8 18 a m	2	50
8 10 a m	3	00

TABLE 3—*Variations in Determinations on Different Individuals*

Subject	Time	Clotting Time	
		Hr	Min
Dr P	4 p m	3	00
Dr P	9 a m	2	55
Miss H	4 p m	3	00
Miss N	4 p m	3	00
Miss S	4 p m	3	00

But, for practical purposes, this is just what is desired Clinically, we are interested, not in the circulating blood so much as in the coagulation of the blood through injured tissue The degree of protection afforded the body by the interaction of all the blood clotting factors is shown by this method and others of like nature

The clotting time of the blood may be accurately determined by this means with such ease and simplicity that there no longer exists any good reason why clinicians everywhere, in hospital, office, or home, should not take advantage, in all indicated cases, of the knowledge thus to be gained



With a clotting time of approximately three minutes, the tube should be inverted every thirty seconds. When it is beyond from five to six minutes, it should be inverted every minute, and when less than two minutes, every twenty seconds. The simplicity of the method permits the making of two or three determinations without discomfort to the patient, so that results may be compared and averaged. As a rule, the different readings do not vary more than twenty seconds.

The normal clotting time with this method depends on several factors, such as the time of day when the determination is made, the length of time since the last meal and the nature of this meal. Mills and Nakayama<sup>4</sup> have found that the normal clotting time with no food in the gastro-intestinal tract is usually from three to three and a half minutes by this method. For from one to three hours after each meal, it is lowered to from one and one half to two minutes, rising again to

TABLE 1—*Determination of Clotting Time*

	Clotting Time	
	Hr	Min
Sept 10, 1922		
7 30 a m (before breakfast)	3	10
11 30 a m (only water since rising)	3	00
12 30 p m (luncheon)		
2 20 p m	2	40
3 20 p m	2	15
6 00 p m	3	00
Sept 11, 1922		
8 00 a m (only water)	3	30
8 10 a m (breakfast)		
9 15 a m	2	00
11 45 a m	3	40

three minutes, usually before the next meal. So it is evident that the clotting time depends greatly on the time of making the determination, as shown in Table 1. It is advisable to determine the clotting time always at the same time of day, either before breakfast or just before some other meal. In this way, the clotting time, uninfluenced by digestion, food, etc., can be determined for comparative purposes over a long period of time. This clotting time, to which the blood reverts after each meal, may be termed the basal clotting time.

In Table 1, we submit the results of a few determinations demonstrating these statements.

To show that these are not accidental variations, we submit in Table 2, a series of determinations (Sept 13, 1922) on the same individual, showing how constant the clotting time is under the same conditions.

Another series of determinations made on different individuals at the same time of day show only slight variations. All these persons

<sup>4</sup> Mills, C A, and Nakayama, Joseph. The Effect of Food Ingestion on the Clotting Time of the Blood, to be published.

following the use of barium chlorid. Each of the foregoing substances apparently increased the irritability of the heart, thus contributing to the appearance of the irregularity.

From the standpoint of auricular fibrillation, experimental observations on the reaction of the auricles to vagal stimulation are varied, and are apparently conflicting. It is generally known that stimulation of the vagi may alter the auricular action in auricular fibrillation.<sup>7</sup> The auricles dilate, and the movements become smaller and more rapid. In other instances of auricular fibrillation, vagal stimulation may be followed by a normal auricular mechanism.<sup>8</sup> On the other hand, the stimulation of the vagi has been observed to promote or induce an absolute irregularity in the normal by contracting auricles.<sup>9</sup> An auricular fibrillation has even been noted to follow the sectioning of the vagi. Lewis, Drury and Bulger<sup>10</sup> have recently confirmed the foregoing reactions with the exception of the last, and conclude that all are compatible with the circus movement of auricular fibrillation. The four cases presented herewith are of interest in that in each premature contractions were induced by forced breathing. In one, the premature beat appeared after administration of epinephrin. In two, auricular fibrillation followed the administration of epinephrin. In one of the latter, the absolute irregularity was at one time provoked by forced breathing.

#### REPORT OF CASES

CASE 1—*Premature contractions induced by forced breathing and eliminated by atropin.* J. S., aged 31, complained of shortness of breath, palpitation and an occasional irregular action of the heart. He was extremely nervous. The cardiac symptoms dated back to military service. He stated that prior to that time his general health had been very good. His past history was negative for the infections that ordinarily induce cardiac disease. There was no history of real infection, and the Wassermann test on the blood was negative.

The examination was negative except for the heart. The cardiac impulse was well within the nipple line in the fifth interspace. A very faint diastolic murmur was heard to the left of the sternum in the third and fourth interspaces. The heart was extremely irritable. The rate increased to 140 per minute with the hopping test but subsided to 80, the original count, within two minutes. The systolic blood pressure was 130, the diastolic, 80. A premature contraction appeared regularly with forced breathing during expiration. The electrocardiogram taken during deep breathing showed a variation in the duration of the cardiac cycles from 0.68 to 0.95 second. The premature beat occurred during the height of vagal tone (Fig 1, top). This irregularity was eliminated by atropin (Fig 1, bottom). There was in addition some depression

7 Lewis, Thomas. *Heart* **1** 306, 1909-1910. Rothberger, C. J., and Winterberg, H. *Arch f d ges Physiol*. Robinson, G. C. *J Exper Med*, **17** 429, 1913.

8 McWilliams, J. A. *J Physiol* **8** 296, 1887. Hirschfelder, A. D. *Bull Johns Hopkins Hosp* **19** 322, 1908. Cushny, A. R. *Am J M Sc* **141** 826, 1911. Garrey, W. E. *Am J Physiol* **21** 283, 1908.

9 Winterberg, H. *Arch f d ges Physiol* **122** 361, 1908.

10 Lewis, Thomas, Drury, A. N., and Bulger, H. A. *Heart* **8** 141, 1921.

# THE INDUCTION OF PREMATURE CONTRACTIONS AND AURICULAR FIBRILLATION BY FORCED BREATHING

ASSOCIATED WITH A CHANGE IN THE LOCATION OF THE  
PACEMAKER \*

FRED M SMITH, M D, AND WILLSON B MOODY, M D  
CHICAGO

Numerous attempts have been made to produce premature contractions in the experimental animal by the stimulation of the vagus and the sympathetic nerves Rothberger and Winterberg<sup>1</sup> and Kure<sup>2</sup> were perhaps most successful in these experiments The former investigators employed combined stimulation of the vagi and the sympathetic, and the latter stimulated the sympathetic Lewis<sup>3</sup> records one instance in which premature beats followed the stimulation of the left vagus on repeated occasions In a later survey of the subject, Lewis<sup>4</sup> questions the interpretation placed by Rothberger and Winterberg on some of their curves, and calls attention to the very low percentage of positive results obtained by Kure He further points out that, in the large number of experiments in which he has stimulated the vagus under varying conditions, in only one instance did the extrasystoles seem to be related to nerve impulses Lewis thus concluded that experimental observations did not demonstrate that an abnormal action of the cardiac nerves alone was responsible for the premature beat He was, however, of the opinion that nerve impulses might provoke extrasystoles in the heart predisposed to the disorder This conclusion was based on experimental investigations made by Levy<sup>5</sup> and Rothberger and Winterberg<sup>6</sup> The former noted the appearance of premature contraction on stimulation of the sympathetic or on sectioning the vagi after the administration of chloroform The latter produced premature beats by stimulation of the sympathetic

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\* From the Medical Department of Rush Medical College

1 Rothberger, C J, and Winterberg, H Arch f d ges Physiol **141** 343-377, 1911

2 Kure, K Ztschr f exper Path u Therap **12** 389-459, 1913

3 Lewis, Thomas Heart **5** 247, 1913-1914

4 Lewis Thomas The Mechanism and Graphic Registration of the Heart Beat, New York, Paul B Hoeber, 1920, p 345

5 Levy, A G Heart **7** 105-110, 1918-1920

6 Rothberger, C J, and Winterberg, H Arch f d ges Physiol **142** 401-522 1911

The initial electrocardiogram showed a regular rhythm (Fig 2, top) The curve at the bottom was taken twenty minutes after the hypodermic administration of epinephrin, 10 minims (1 1,000 solution) Leads II and III show the effects of deep breathing There are now periods during which there is a definite slowing of the cardiac rate associated with the onset of an idioventricular rhythm and the appearance of premature contractions

*CASE 3—Premature contractions during forced breathing, and auricular fibrillation following the administration of epinephrin* F P, aged 32, complained of an occasional vague distress in the precordial region He was highly nervous, in this respect resembling very much the patients previously considered His past history was negative and there was no venereal infection

The heart was normal in size and there were no murmurs Premature contractions appeared fairly regularly during forced breathing They seemed to occur near the end of the greatest inhibition in the cardiac rate The systolic

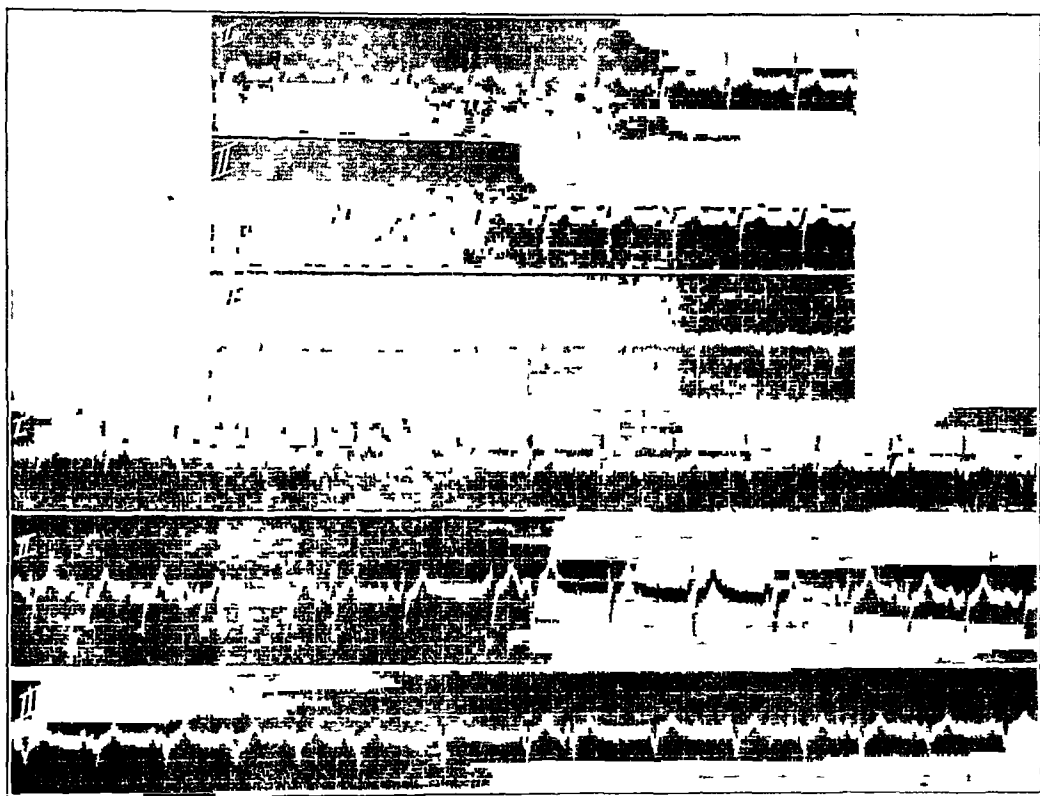


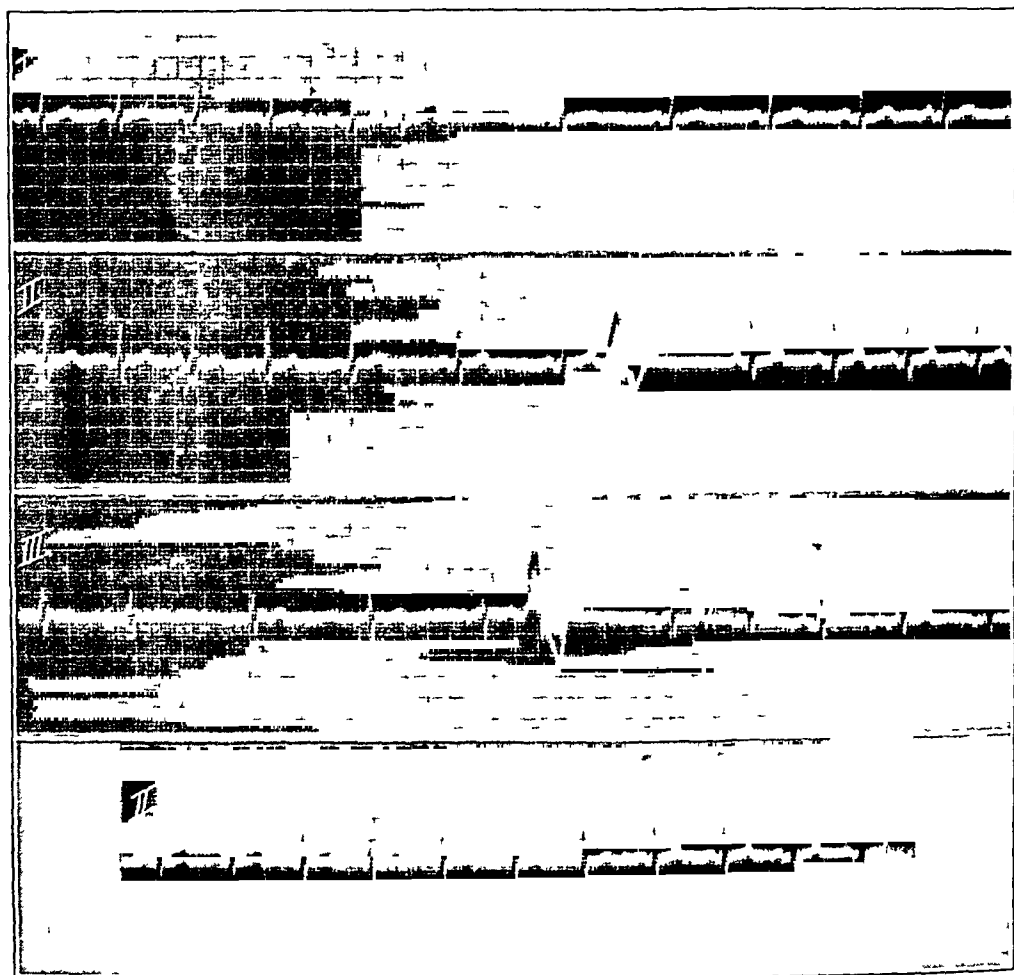
Fig 2 (Case 2) —Top Curve taken during forced breathing Bottom The electrocardiogram was taken twenty minutes after administration of epinephrin Leads II and III show the effect of deep breathing There are periods of inhibition in the cardiac rate during which there is an idioventricular rhythm and premature contraction

blood pressure was 118, the diastolic, 80 The electrocardiogram verified these findings with regard to the extrasystole (Fig 3, top) There was a greater variation in the duration of the cardiac cycles during forced breathing than in the preceding patient The changes in the auricular deflection during the increased vagal tone were similar to those shown by the electrodiagram of the first patient considered There was an occasional instance in which there was no evidence of auricular activity preceding the ventricular deflection Following the electrocardiogram shown in Figure 3 (top), 10 minims (1 1,000 solution) of epinephrin hydrochlorid was given hypodermically In about fifteen minutes, the auricles went into fibrillation (Fig 3, bottom) Vagal

of the auricular wave during vagal inhibition. The auricular deflection was diaphasic in some instances, and was occasionally negative with a shortening of the P-R interval. The change in the auricular phase of the electrocardiogram persisted to some extent after the administration of atropin sulphate, one-fiftieth grain.

**CASE 2**—*Premature contractions and idioventricular rhythm during forced breathing following administration of epinephrin.* W. K., aged 22, complained of nervousness and occasional cardiac irregularity. His past history was negative, and the Wassermann test of the blood was negative.

The apex impulse was 1 cm. outside the nipple line in the fifth interspace. A soft diastolic murmur was heard to the left of the sternum in the third and fourth interspaces. The systolic blood pressure was 130, the diastolic, 70.



**Fig 1 (Case 1)**—Top. The three leads were taken during forced breathing. The duration of the cardiac cycles in Lead I varies from approximately 0.68 to 0.95 second. In each lead is shown a premature contraction which appears during vagal inhibition. A change in the form of the auricular deflection is noted in Leads II and III. In Lead II, the second and fourth are depressed. The third seems diaphasic and the fifth is apparently negative. In Lead III, there is only one positive auricular wave, and it appears during the accelerated period. Bottom. Lead II was taken during forced breathing twenty minutes after the administration of atropin sulphate, one-fiftieth grain. The extrasystole has disappeared, but the change in the auricular deflection persists.

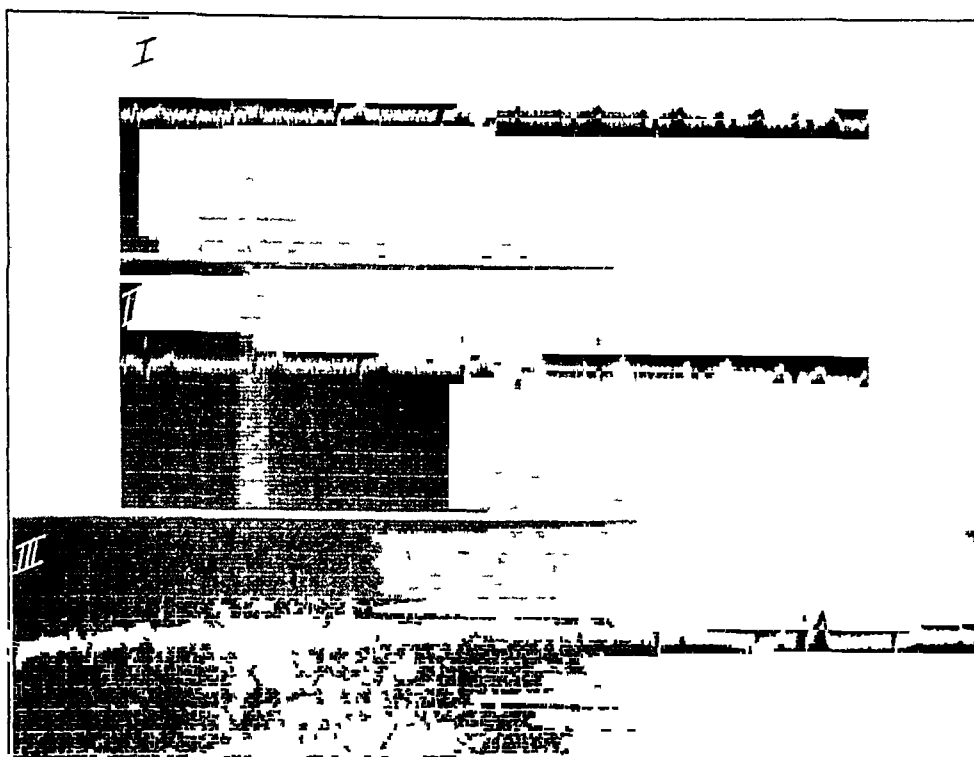


Fig 4 (Case 4) —Leads I, II and III taken during forced breathing In each lead a premature contraction occurs during the period in which there is an inhibition in the cardiac rate Preceding the appearance of the extrasystole, there are changes in the form of the auricular deflection

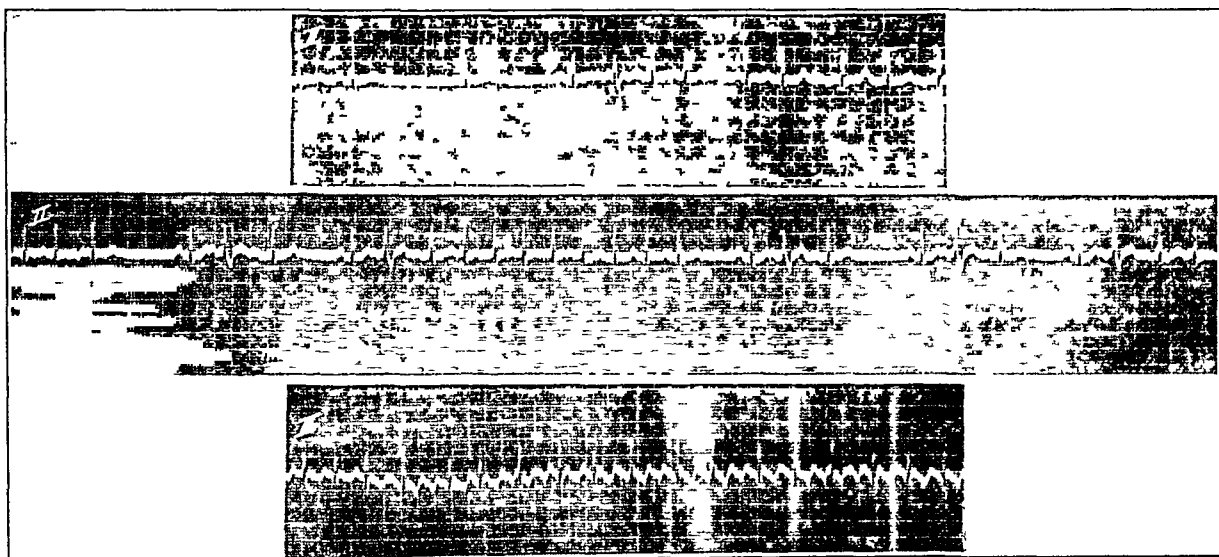


Fig 5 (Case 4) —Top Lead II The onset of auricular fibrillation induced by deep breathing Middle Lead II The auricular fibrillation induced by epinephrin was broken up into short paroxysms by combined pressure over the carotid sheaths and forced breathing The normal auricular mechanism was restored for a few cycles during expiration It is observed that premature contraction appeared during this period It is to be further noted that the onset of the absolute irregularity is preceded by an extrasystole Bottom Lead II The auricular mechanism resembles that of flutter The record was taken after the administration of physostigmin, one seventy-fifth grain

stimulation by forced breathing and by pressure on the eyes and the carotid sheaths apparently did not influence the absolute irregularity. The auricular fibrillation continued for about two hours.

CASE 4—*Premature contractions and auricular fibrillation following deep breathing* F W, aged 39, consulted a physician because of attacks of rapid action of the heart. These attacks had occurred at infrequent intervals for about two years. They had repeatedly been observed to appear during periods of excitement and high nervous tension. He had recently been compelled to take a physical examination for a position, and had been fearful that he might

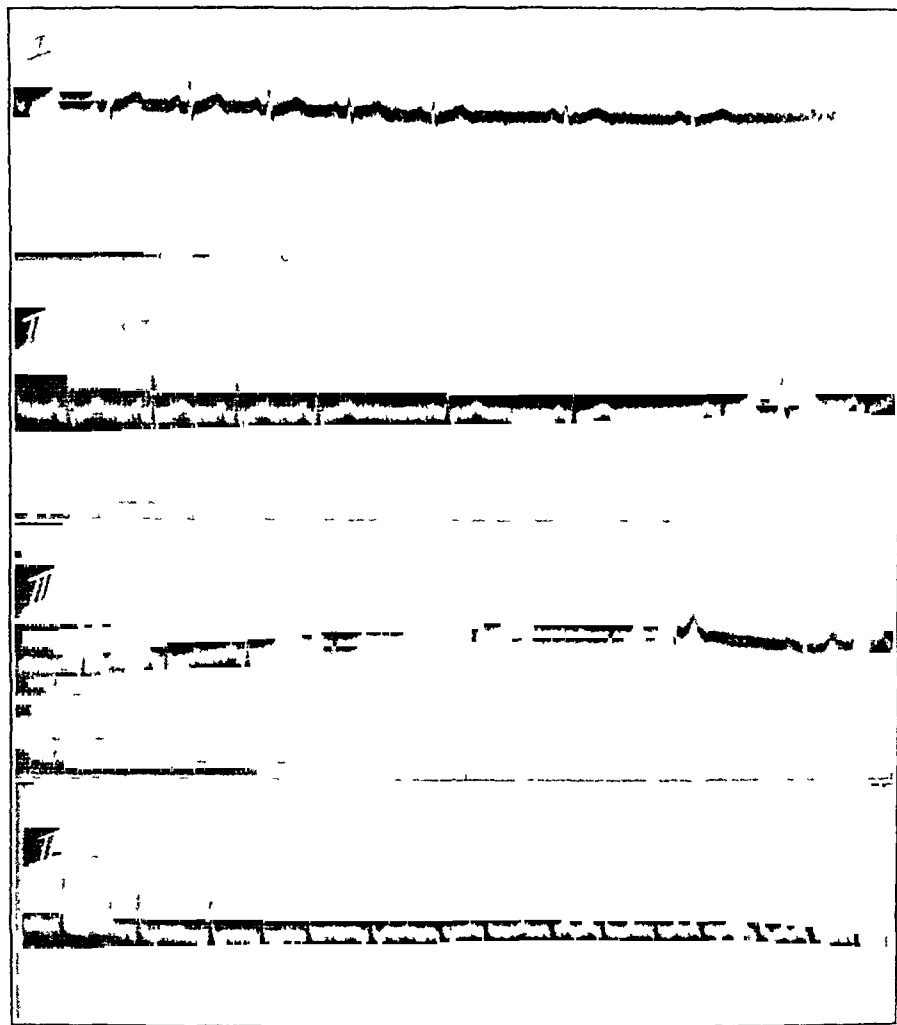


Fig 3 (Case 3)—Top The record was taken during forced breathing. In Leads II and III, premature beats appear near the end of vagal inhibition. Changes in the auricular deflection are also noted, particularly in Lead III. The fifth auricular complex is a slightly negative phase. In the sixth cardiac cycle, there is no evidence of auricular activity preceding the ventricular deflection. Bottom Lead II shows an auricular fibrillation following the administration of epinephrin, 10 minims (1:1000 solution).

not pass the physical test because of the possible onset of the tachycardia. No sooner had he presented himself for the examination than an attack occurred. The examining physician noted that the cardiac rate was extremely rapid and the rhythm apparently absolutely irregular. The attack ended abruptly shortly after the examination.

The migration of the pacemaker from the sinus to the auriculoventricular node may be sudden or gradual. If the former, there is an abrupt change in the auricular complex from a positive to a negative form, with a shortening of the P-R interval. If the latter, the auricular wave may be flattened or become diaphasic before it finally reaches the negative phase. During the intermediate changes from the positive to the negative form, the impulse may arise from both the sinus and auriculoventricular nodes. There is an occasional instance in which there is no evidence of auricular activity preceding the ventricular deflection. It is believed that under these circumstances the pacemaker may have migrated to a lower level in the auriculoventricular node, or there even may be an escape of an idioventricular rhythm.

The mechanism responsible for the change in the location of the pacemaker in the second patient is apparently different from that in the three patients previously considered. The opposing actions of the vagi and sympathetic nerves in the patient were well balanced under normal conditions even with deep breathing (Fig 2, top). After the administration of epinephrin the action of these nerves was markedly deranged. It will be noted that there are periods of inhibition in the cardiac rate during which there is an escape of an idioventricular rhythm resulting in a dissociation of the auricles and ventricles (Fig 2, bottom). It would seem that the phenomena might be explained on the basis of a combined stimulation of the vagi and sympathetic by the epinephrin, in which the abnormal action of the former is manifested chiefly on the sinus node, whereas that of the latter increases the inherent rhythm of the ventricles. In the experimental animal, an inhibition of the cardiac rate has frequently been observed following the administration of epinephrin. This was explained on the basis of vagal stimulation.

An idioventricular rhythm occasionally follows the administration of atropin. Wilson<sup>15</sup> and White<sup>12</sup> have each reported a patient in whom this phenomenon was observed. In each instance, there was a delayed conduction of the auriculoventricular bundle. The curves shown in Figures 6 and 7 are of particular interest in this connection, in that the auriculoventricular dissociation resulting from a recurring cardiac infection was later reproduced by administration of atropin. The electrocardiogram in the case of this child first showed a prolongation of the P-R interval similar to that in (Fig 6, bottom). Later, there was an auricular ventricular dissociation (Fig 6, top). After about two months, the sinus rhythm was again established (Fig 6,

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15 Wilson, F. N. The Production of Atrioventricular Rhythm in Man After the Administration of Atropin, *Arch Int Med* **16** 989 (Dec.) 1915



The general health had been very good. There was a history of typhoid fever in childhood, but no other serious illness, rheumatism, a relative freedom from sore throats, and no venereal infection. The Wassermann test on the blood and spinal fluid was negative. The teeth had recently been roentgen rayed. Five were found to have apical infections and were extracted. The patient was accepted for life insurance in 1920. The examining physician noted a rapid cardiac rate and requested that he return for another pulse reading.

The patient was more than 6 feet tall and weighed 190 pounds (86.4 kg). He appeared to be in excellent general health. The physical examination was negative except for the heart, which was normal in size and without murmurs, but during ordinary breathing showed a slight waxing and waning of rate. The patient was requested to breathe deeply. Short attacks of rapid irregular heart action appeared during expiration (Fig 5, top), persisting as long as the forced breathing was continued but subsiding as soon as normal respiration was established. The patient was very anxious about the condition of his heart. He had had little sleep for several nights and was extremely nervous. He was encouraged and told to forget the heart, and was asked to return in one week. He apparently placed absolute confidence in the advice and began at once to sleep soundly through the night. One week later, he returned for further observation. The nervousness had subsided and he had no further trouble with the heart. We were unable to produce the auricular fibrillation by forced breathing, but premature contractions occurred regularly at the height of vagal inhibition (Fig 4). The patient was then given 10 minims (1,000 solution) of epinephrin, hypodermically. At the end of twenty minutes, an extremely rapid, irregular cardiac rhythm was precipitated by forced breathing. Unfortunately, the onset of the auricular fibrillation was not caught by the electrocardiograph. Later, on forced breathing, the irregularity occurred in short paroxysms (Fig 5, center). The normal auricular mechanism was restored for a few cardiac cycles during the period of greatest vagal inhibition, produced by pressure over the carotid sheaths at the time of expiration. The patient was then given physostigmin, one seventy-fifth grain. The electrocardiogram taken twenty minutes later showed auricular flutter (Fig 5, bottom). We may add that this patient also had changes in the auricular deflection of the electrocardiogram, with expiration during the period of normal auricular mechanism.

#### COMMENT

The changes that occurred in the auricular deflection of the electrocardiogram of three of these patients have been described by Wilson,<sup>11</sup> White<sup>12</sup> and others. Similar variations in the auricular wave have been produced experimentally in animals by Lewis and his co-workers<sup>13</sup> and by Meek and Eyster.<sup>14</sup> The mechanism of this phenomenon in man is dependent on an increased action of the vagus nerves on the sinus node over that on the lower rhythmical centers, and is comparable to that produced experimentally in animals by the stimulation of the right vagus. The rate of the sinus node is sufficiently decreased to permit the escape of the auriculoventricular node as the pacemaker.

11 Wilson, F. N. Three Cases Showing Changes in the Location of the Cardiac Pacemaker Associated with Respiration, *Arch Int Med* **16** 86-97 (July) 1915.

12 White, P. D. Ventricular Escape, *Arch Int Med* **18** 244 (Aug.) 1916.

13 Lewis, Thomas, Meekins, J., and White, P. *Phil Tr Roy Soc, London, Series B* **205** 375, 1914.

14 Meek, W. J., and Eyster, J. A. E. *Heart* **5** 227-246, 1913-1914.

bottom) At this time, the child was given 1/300 grain atropin sulphate, hypodermically The electrocardiogram taken twenty minutes later showed an auriculoventricular dissociation (Fig 7) Wilson has explained this reaction on the basis of an unequal distribution of the action of atropin on the vagus endings He considered that those fibers which supply the auriculoventricular bundle were perhaps paralyzed first This, in turn, permitted the escape of a ventricular rhythm, resulting in a dissociation of the auricles and ventricles The observation in this patient suggests that vagus action on the auriculoventricular bundle might have been deranged by the infection

In each of the first four patients, the premature contractions were induced by forced breathing They regularly appeared during the period of the inhibition of the cardiac rate It would thus seem that the stimulation of the vagi incident to deep breathing influenced the appearance of the irregularity It would also seem that an increased sympathetic tone may perhaps be a contributory factor, since in one instance the premature beat appeared after the administration of epinephrin It is very doubtful that the nerve stimulation was entirely responsible for the irregularity, since the patients, according to their history, were apparently predisposed to disorder This conception is in accord with the results of experimental investigation<sup>16</sup> It is to be recalled that the production of premature contractions in the experimental animal by stimulation of the cardiac nerves alone has been unsuccessful, whereas the results have been positive after the heart was predisposed to the disorder by the administration of chloroform and barium chlorid

In two of the patients, paroxysmal auricular fibrillation was observed Neither of these patients had the cardiac pathology usually associated with an auricular fibrillation In each, the heart was apparently normal in size In each instance, the absolute irregularity was induced by epinephrin In one, the auricular fibrillation was at one time provoked by forced breathing The latter feature was observed when the patient was extremely anxious about his condition A few days later, after the nervousness had subsided, the irregularity could not be produced by deep breathing alone but only after it was induced by epinephrin It is to be further recalled that the paroxysmal auricular fibrillation frequently occurred during periods of excitement While the disorder was influenced by the strong inhibitory action of the vagi, it was also apparently dependent on the state of the sympathetic tone Thus, when the sympathetic tone was high, vagal stimulation favored the entrance of the state of rapid reexcitation responsible for the auricular fibrillation

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16 Lewis, Thomas Footnotes 5 and 6

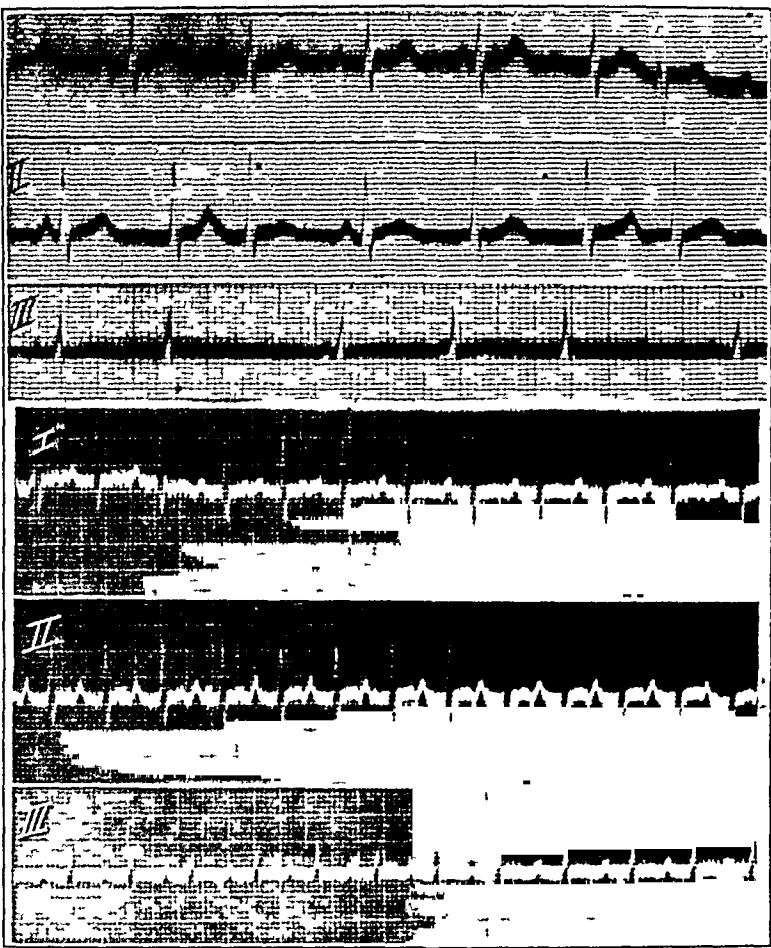


Fig 6—Top Dissociation between the auricles and ventricles In the first three cycles of Lead I, the ventricles are responding to sinus impulses Bottom A prolongation of the P-R interval

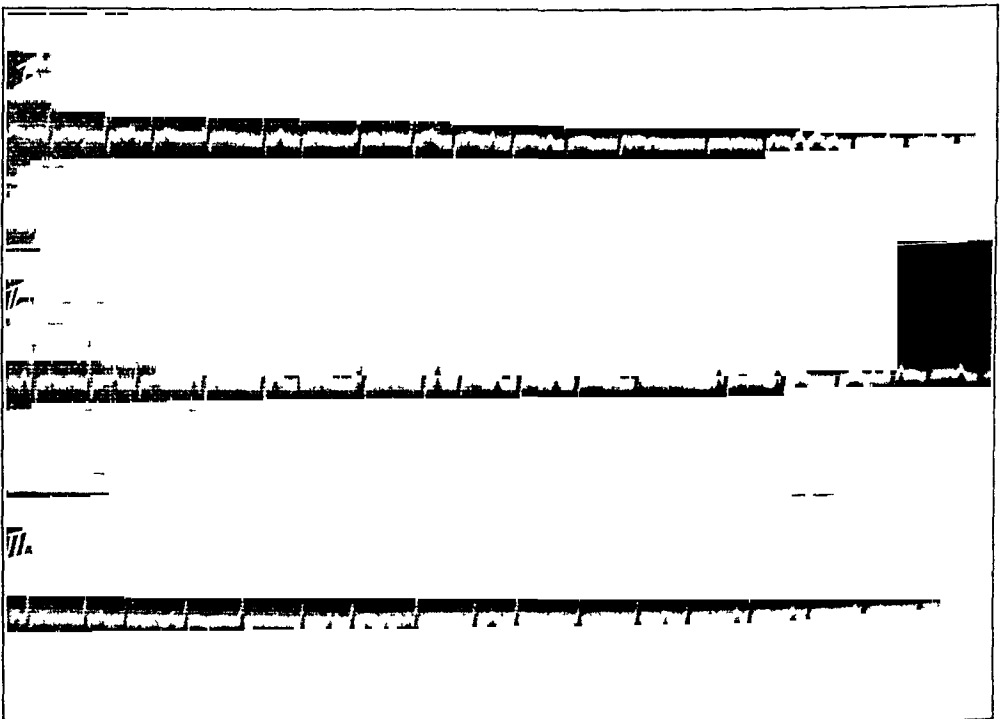


Fig 7—This curve was taken twenty minutes after the administration of atropin The condition resembles that shown in Fig 6 (top) In the middle of Lead II there are three cycles of sinus rhythm

# THE RELATIONSHIP OF EXCESS OF URIC ACID IN THE BLOOD TO ECZEMA AND ALLIED DERMATOSES

BASED ON AN ANALYSIS OF OVER TWO HUNDRED CASES

JAY F SCHAMBERG, M D

Director, Research Institute of Cutaneous Medicine

AND

H BROWN, B Sc

Chemist, Research Institute of Cutaneous Medicine

PHILADELPHIA

The present study was undertaken for the purpose of shedding some light on the etiology of diseases of the skin of obscure origin. It was soon found that special interest was attached to the findings in eczema. For this reason, a special study was made of this disease, which comprises over one half of the analyses made.

Cases of eczema constitute almost one third of the cases of diseases of the skin. This disease commonly causes keen distress by intolerable itching. Sleep is interfered with, the nervous system greatly disturbed and life often made almost unbearable. The causative factors in the production of eczema have for a century been obscure. All sorts of hypotheses have been advanced, advocated, discussed, and most of them have been discarded to make way for new suppositions. The Vienna School under the leadership of Hebra held that the dominant causes of eczema were local, whereas the French school conjured up hereditary or acquired diatheses to explain the origin of this disease. It must be recognized that eczema is not a simple entity, but a type of reaction in the skin possessing certain clinical features. These features are not sufficiently distinctive to enable one to distinguish the etiologic factors involved. It is often impossible to differentiate between a chronic dermatitis due to local irritants and a true eczema of constitutional origin. There is an almost general agreement today concerning some causes of eczema. It is acknowledged that among etiologic factors may be classed intestinal toxemia, protein sensitization (both food and other proteins), endocrine disorders, disturbances of the nervous system, hyperglycemia, and other conditions. The older writers, particularly among English dermatologists, laid considerable stress on the association of gout and eczema. The urinary analyses and the laboratory data on which this origin of eczema was predicated were, however, regarded as so loose and unscientific as to lead to a progressively growing incredulity concerning this alleged relationship. In four out of six American treatises on dermatology published within recent years, no

So far as we know, Stokes<sup>17</sup> has reported the only other instance in which forced breathing induced auricular fibrillation. An additional feature in our patient was the precipitation of the disorder by epinephrin and excitement. Kuré<sup>18</sup> has recorded a patient in whom paroxysmal tachycardia was induced by excitement. He was able to produce the tachycardia by compelling the child to concentrate on a problem in mental arithmetic. Lewis<sup>4</sup> states that he has observed similar but less striking examples of the latter feature. In this connection, it may be added that Galli<sup>19</sup> has reported an instance in which paroxysmal tachycardia followed the administration of atropin. The patient was, however, subject to the condition

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17 Stokes, K. H. *Heart* **1** 297-305, 1909-1910

18 Kure, K. *Deutsch Arch f klin Med* **106** 33-46, 1912

19 Galli. *Heart* **7** 111 (April) 1920

but they were taken at random among laboratory workers and presumably were normal

In patients presenting themselves with various dermatoses, different findings are encountered. Of 163 patients, eighty-eight, or 53.6 per cent had more than 3 mg of uric acid. Fifty patients, or 30.5 per

TABLE 1—*Normal Values of Human Blood in Milligrams per 100 c c*

Nonprotein Nitrogen	Urea Nitrogen	Uric Acid	Sugar	Authority
30-45	15-25	1.0-3.5	50-120	Gettler and Baker J Biol Chem <b>25</b> 211, 1916
22-37	12-27	0.7-3.7	95-110	Fohn and Denis J Biol Chem <b>14</b> 29, 1913
30	6-20		100-110	Greenwald J Biol Chem <b>21</b> 61, 1915
19-39				Bang Blochem Ztschr <b>72</b> 104, 1915
25-28				Taylor and Hutton J Biol Chem <b>22</b> 63, 1915
23-44	12-27	1.0-2.0	90-110	McLean and Selling J Biol Chem <b>19</b> 31, 1914
25-30	12-15			Meyers and Fine Post Graduate, N Y, 1914-1915
	10.8-25.2			Hohlweg Med Klin Wehnschr, 1915, p 331
		2.5		Schwartz and McGill Arch Int Med <b>17</b> 42 (Jan) 1916
				Moose and Zondek Munchen med Wehnschr <b>62</b> 1110, 1915
			90-110	Lewis and Benedict J Biol Chem <b>20</b> 61, 1915
			90-130	Michaelis Blochem Ztschr <b>59</b> 166, 1914
			40-120	Strouse Bull Johns Hopkins Hosp <b>26</b> : 211, 1915

TABLE 2—*Blood Values from Normal Persons \**

No	Name	Age	Weight in Kilo grams	Non protein Nitro gen	Urea Nitro gen	Sugar	Uric Acid	Creat inin
1	H R	24	70.0	30	13	104	2.0	1.4
2	J K	19	61.4	30	13	110	1.9	1.3
3	W B	21	61.4	26	13	110	1.8	1.4
4	H B	25	61.4	31	15	93	2.2	1.5
5	A K	30	86.4	34	17	109	3.5	1.4
6	B F	23	61.8	27	13	120	1.9	1.6
7	J S			31	10	66	3.1	1.3
8	J T	35	70.0	36	18	107	3.4	1.0
9	J H	22	66.8	35	12	101	2.3	1.5
10	Miss W	22	56.4	35	10	96	2.8	1.1
11	Miss M	18	59.1	36	14	99	2.8	
12	Miss B	18	57.7	35	13	105	3.2	
13	Mrs J	26	56.8	31	14	100	1.8	1.3
14	Miss R	25	54.5	37	16	103	3.1	1.5
15	Miss K			38	18	110	3.0	1.2
16	J M	22	66.0	33	13	96	2.9	1.1
17	Miss S	32		37	18	102	1.3	1.3

\* Seventeen cases between the ages 18 to 35, average uric acid, 2.5 mg

cent, had 4 mg or more. Eighteen patients, or 11 per cent, had 5 mg or more, and seven patients, or 4.6 per cent, had 6 mg or more.

Of 164 patients, ninety had eczema, and of these sixty, or 66.6 per cent, had over 3 mg of uric acid per 100 c c of blood. Thirty-five patients, or 39 per cent, had 4 mg or more of uric acid, fifteen patients, or 16.6 per cent, had 5 mg or more, and six patients, or 6.6 per cent, had 6 mg or more.

mention of gout or uric acid in relation to eczema is made, and scant attention is paid to renal insufficiency

#### FINDINGS IN CHEMICAL STUDIES OF THE BLOOD

As our blood analyses accumulated, it became evident that in the group of cases studied by us, the blood sugar was almost invariably within normal limits. The average content of sugar in 166 cases was 101 mg. It varied between 65 mg and 160 mg per 100 c c of blood. In two cases—a case of eczema and a case of psoriasis—it was 160 and 146 mg, respectively, but these figures although above the average were possibly not beyond normal limits. In only one case was the sugar content of pathologic significance. This was in a woman, 70 years of age, who had had generalized itching for twenty years, and who presented an erythematous eczema of the legs, with vulvar and vaginal pruritus. She had 273 mg of sugar per 100 c c of blood. The urine was free from sugar, but there was a history that glucose had been found in the urine on former occasions. On a diabetic regimen, the pruritus promptly improved almost to the point of disappearance.

#### URIC ACID

In the course of our studies, it soon became evident that the most significant finding was a variation from the normal of the uric acid content. It is, of course, a matter of the greatest importance to possess an accepted standard of the maximum normal amount of uric acid in the blood.

In 1913, Folin and Denis<sup>1</sup> wrote that the normal uric acid content in healthy adults was usually between 2 and 3 mg per 100 c c, but that strictly normal persons might have as low as 1 mg and as high as 3.5 mg, the differences probably depending in part on dietary factors. Nine years later, Folin<sup>2</sup> writes: "The maximum normal figure for uric acid may be perhaps given as 3 mg per 100 c c\*." Others investigators have given estimates of the normal limits which are presented in the subjoined table.

In order to check our results, we examined the blood of seventeen presumably normal persons. It so happened that these were all young adults varying in age between 18 and 35 years. The uric acid content varied between 1.3 and 3.5 mg and averaged 2.5 mg.

Of this number, one had 3.5 mg, one 3.4, one 3.2 mg and two 3.1 mg. It is not known that all of these subjects were entirely normal,

1 Folin, O. *J Biol Chem* **14** 29, 1913

2 Folin, O. *Physiol Rev* **2** 460 (July) 1922, quoted from the article of Meyers, Fine and Lough (footnote 3)

\*In a private communication received by us in April 1923, from Dr. Folin, he writes "The upper normal values for uric acid are probably a little higher than we have thought."

TABLE 3—*Age Incidence in Eczema \**

11-20	21-30	31-40	41-50	51-60	61-70	71-80
20	54	33	22	33	44	33
46	27	33	39	48	58	22
31	28	55	29	27	56	48
24	24	33	24	47	40	35
21	22	18	41	38	32	
29	40	22	53	38	39	
37	21	36	64	24	26	
	28	28	36	25	39	
		39	48	34	62	
		29	31	36	50	
		43	49	31	48	
		26	34	42	62	
		27	24	16	23	
		34	23	52		
		32	31	63		
			45	35		
			22	51		
			49	29		
			40	34		
			49	28		
			40	63		
			41	39		
			59	26		
			30			
			43			
297	3005	302	386	386	445	333

\* Tables 3, 4 and 5 and the chart do not include the entire 200 cases studied, they were completed prior to a number of the later analyses

TABLE 4—*Dermatoses, Excluding Eczema, Age Decades*

11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
25	23	23	23	35	33	47	18
44	28	32	28	27	21	47	
26	24	28	23	27	52		
	33	25	33	47	30		
	28	66	30	39			
	30	26	31	39			
	17	28	40	25			
	40	22	32	33			
	38	22	31	31			
	31	50	26	38			
	41	35	22	31			
		43	46	24			
		29	44	42			
		50	28	29			
		31	23	40			
		48	40				
		47	40				
		22	45				
32	303	348	325	338	34	47	18

TABLE 5—*Effect of Age on Uric Acid Content of Blood*

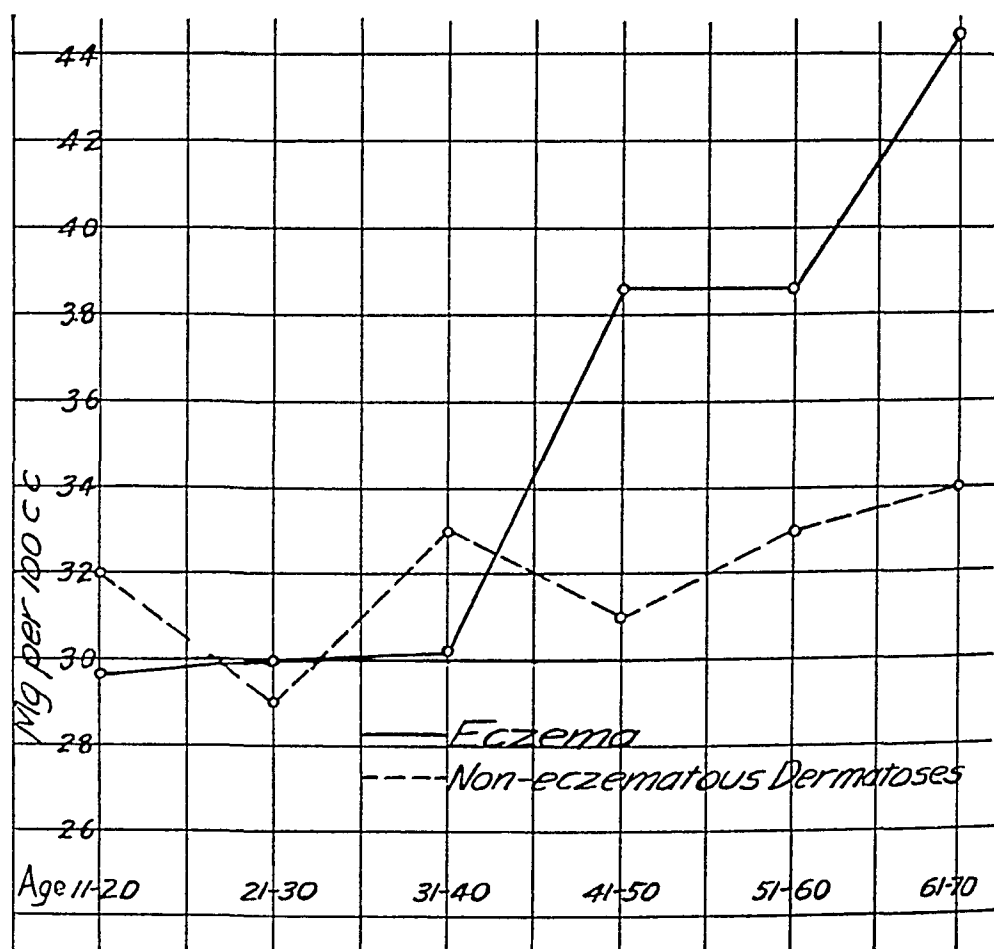
Noneczematous			Eczema		
Age	Mg	No. of Cases	Age	Mg	No. of Cases
11-20	3.2	3	11-20	2.97	7
21-30	2.9	10	21-30	3.005	8
31-40	3.3	13	31-40	3.02	15
41-50	3.1	16	41-50	3.83	25
51-60	3.3	12	51-60	3.86	23
61-70	3.4	4	61-70	4.45	13
			71-80	3.33	4



It is thus seen that the incidence of hyperuricemia is higher in eczema than in other dermatoses. If it should be held that 3.5 mg of uric acid is within normal limits, then computation discloses that 45, or 50 per cent, of the patients had a higher uric acid content than this amount.

#### EFFECT OF AGE ON URIC ACID CONTENT IN BLOOD

There can be no doubt that age has an important influence on the amount of uric acid in the blood.



Effect of age on uric acid content of blood

Ninety-five cases of eczema and eczematoid conditions were studied. If these are classified according to age decades, it is seen that there is a gradually rising incidence in the uric acid figures (Tables 3, 4 and 5) from 20 up to 70 years. If we compare the noneczematous dermatoses with the cases of eczema, a striking contrast in the curve is seen. The average of the various age decades comes close to normal figures and does not exhibit any rising curve.

In the group designated eczema are unquestionably included a considerable number of cases which are eczematoid in nature, but doubt

doubt that some of the cases represent instances of interstitial nephritis. In cases in which the nonprotein nitrogen and the urea nitrogen are high, the high uric acid figure is readily explained. But there are many cases among those studied by us in which the nonprotein and urea nitrogen were clearly within normal limits.

*Creatinin*—It is interesting to note that in not a single patient was the creatinin in excess of the normal figure. Indeed, it varied within narrow limits, between 1 and 1.9 mg. In a case of nephritis in which the analysis was made in another laboratory but included in our series, it was 2.8 mg.

The low creatinin values are to be explained on the basis that our patients were not sick in the ordinary sense of the word, and retention of creatinin occurs only in fairly well advanced nephritis.

TABLE 6—Average Amount of Uric Acid in Blood in Different Dermatoses

	Number of Cases	Average Uric Acid per 100 C c of Blood, Mg
Psoriasis	11	3.2
Pruritus (local and general)	11	3.2
Acne	3	3.0
Urticaria	4	3.08
Eczema	95	3.8

CASE 1—K. B., aged 22, a flabby young man who was overweight, had suffered for three years with violent itching of the face and of the upper part of the torso, with secondary eczema induced in part by irresistible scratching. His sleep was greatly disturbed.

This patient had 5.4 mg of uric acid per 100 c c of blood, with 30 mg of nonprotein nitrogen and 13 mg of urea nitrogen. The urine was free from albumin and casts and had a specific gravity of 1.030. The blood pressure was 130.

Under a dietary regimen eliminating foods containing purin, there was an immediate and remarkable improvement in the itching and the eruption.

CASE 2—W. S., aged 17, who weighed 130 pounds (60 kg.), suffered from a vesiculosquamous eczema of the hands at various intervals for six years. Blood analysis revealed 4.6 mg uric acid, 35 mg nonprotein nitrogen and 18 mg urea nitrogen. This was the most youthful patient in our series with a high uric acid content in the blood. The eruption disappeared in a short time.

CASE 3—A. McL., aged 40, was supposedly suffering from a trinitro-toluene dermatitis of the face and hands due to contact with this substance during the war. The entire face was red, swollen and weeping. The case proved utterly refractory to all types of local medicaments applied over a period of many months.

The blood showed the presence of 5.5 mg of uric acid, 32 mg of nonprotein nitrogen and 13 mg of urea. The blood pressure was 135 mm. The specific gravity of the urine was 1.010, there were no albumin or casts.

The patient has been placed upon a proper dietary regimen and virtually cured.

CASE 4—I. P. H., a man, aged 39 years, with a recurring markedly itching eczema of the legs, had had generalized outbreaks during the last three summers. The blood analysis gave the following figures: uric acid 4.3 mg, nonprotein nitrogen, 36 mg, urea nitrogen, 16 mg. The father, mother and grandfather had gout. The youngest of five children had eczema. On appropriate diet and local treatment, great improvement occurred.

exists as to whether they constitute cases of genuine eczema. In many of these cases there are normal blood uric acid values. We have included them in order not to be guilty of any manipulation of the statistics.

For the most part, young patients with eczema have a normal amount of uric acid but there are several notable exceptions to this statement.

*Pruritus*—In several of our cases of generalized pruritus in young persons there have been high uric acid values in the blood, in one there were 5.4 mg and in another 4.7 mg. These cases are of particular interest.

*Psoriasis*—Most of the patients with psoriasis had normal uric acid figures. In a few persons past middle age, the figures were high, but we believe that this was due to the coexistence of a renal condition and that it did not bear any causative relation to the cutaneous disease. The average uric acid in fourteen cases of psoriasis was 3.2 mg per 100 c c of blood. The average age of these patients was 46 years.

#### INFLUENCE OF SEX ON URIC ACID IN BLOOD IN THE CASES OF ECZEMA

The average blood uric acid for male patients with eczema in our series was 4.16 mg per 100 c c, and the average for the females was 3.08 mg.

The average age of all the males whose blood was analyzed by us was 49.8 years, and the average age of the females was 42.1 years. The difference in age is not sufficient to explain a difference of 25 per cent in the uric acid content. Some other factor or factors must be invoked. The fact that men are bigger eaters and larger consumers of flesh foods and alcohol than women must, we believe, be taken into consideration. The average weight of men would also be greater than the average weight of women.

#### TYPE OF PATIENTS STUDIED

The persons studied were all private patients from the middle and higher walks of life. They were all ambulatory or office patients and sought medical advice primarily for some cutaneous disorder. They ranged in age from 14 to 85 years, but by far the largest number fell within the decades from 30 to 60 years. The blood was taken within two to three hours after a light breakfast.

The data already submitted indicate that there is a high incidence of hyperuricemia associated with the eczema. This is the particular finding that we desire to present. As to the interpretation of this hyperuricemia there may be differences of opinion. There can be no

urine showed a trace of albumin and hyaline casts. The blood findings were uric acid, 24, nonprotein nitrogen, 36, urea, 16, sugar, 110.

Here the blood would indicate perfectly normal kidneys, and yet the urine would hardly support such a contention.

CASE 13—W. L. B., a woman, aged 55, nine months ago developed an eczema which has now become a universal exfoliative dermatitis. She had albumin and casts in the urine, and suffered retinal hemorrhages. The blood pressure at one time was 200. The blood findings were uric acid, 54, nonprotein nitrogen, 35, urea, 16, and sugar, 144.

The nonprotein nitrogen and urea were normal, but the uric acid was very high. This case emphasizes, as do many others, the fact that uric acid first accumulates in the blood as a result of damaged kidneys. At the present time, the blood pressure is 155, and there is no albumin or casts in urine.

Instead of finding urinary evidence of kidney disease with low urea and nonprotein nitrogen figures, the reverse situation may be encountered.

CASE 14—M. W., a man, aged 42, had a disease diagnosed as recurrent vesicular eczema of the hands. The blood revealed uric acid, 49, urea, 20, and nonprotein nitrogen, 46. Urine examination revealed specific gravity 1.018, no albumin or casts.

It would seem probable that this patient had renal disease.

Other cases of a similar character might be quoted.

Apparently diet is an influencing factor in some cases in the causation of hyperuricemia. One of the highest uric acid figures that we have observed was in a meat dealer, aged 42, suffering from eczema, who was in the habit of eating from three to four pounds (1.3 to 1.8 kg.) of red meat a day. His blood showed uric acid, 64, urea, 16, and nonprotein nitrogen, 40.

On the other hand, those who are small eaters and live largely on a nonflesh diet, quite commonly have low nitrogenous blood values. A thin woman, aged 85, very careful of her diet, had only 18 mg. uric acid in her blood.

#### DISCUSSION

A survey of the cases cited reveals the fact that a high percentage of persons suffering from certain dermatoses, particularly eczema, have a hyperuricemia.

The question of an etiologic relationship between the uric acid and the associated dermatoses is a pertinent one. Gout and the uric acid diathesis were for many years invoked as the causes of many disorders, including a variety of diseases of the skin. The incrimination of uric acid in the blood as a cause of eczema is commonly found in the older textbooks. Let us quote an excerpt from the work of an eminent English dermatologist writing nearly forty years ago. Tilbury Fox, in 1884, in his treatise on "Diseases of the Skin," says

All disorders which are connected with the excreta in the system and their circulation throughout the blood current may furnish the exciting cause of eczema. This is a clinical fact of great importance. Given the tendency to eczema then the transmission of uric acid to the capillaries of the skin will so far derange as to aggravate, certainly, and now and again excite an eczematous eruption. This is what is meant by gouty eczema. By securing the absence of uric acid from the circulation the eczema will often disappear and always be more amenable to treatment. The passage of uric acid through the cutaneous capillaries of an eczematous subject acts as much the part of an irritant as do some externals. A gouty state of the blood may, therefore, excite and modify

CASE 5—H C D, aged 41, had suffered for some years from an erythematopapular eczema involving the forehead. Despite various forms of treatment, including the use of the roentgen ray, recurrences have developed. Examination of the blood disclosed the following findings:

Uric acid, 48 mg, nonprotein nitrogen, 33 mg, urea nitrogen, 14 mg

An appropriate diet has been outlined for the patient, and he is at present free from the eruption.

CASE 6—J E F, aged 35, sought medical advice for persistent areas of exfoliative glossitis of five months' duration, presenting somewhat the appearance of the "geographic tongue." His general health was excellent. The Wassermann test was negative. Examination of the blood revealed the presence of 5 mg of uric acid, 36 mg of nonprotein nitrogen and 16 mg of urea nitrogen. This is the only case of this character in which a blood analysis has been made by us. The etiology of this curious condition has been entirely obscure.

CASE 7—Mrs K G S, aged 44, had vesicular eczema on the hands and fingers and an erythematous eczema on the face. She had four or five attacks, the last of which occurred three years ago. She had had one child. The patient felt tired and "dragged" in the mornings. Blood analysis revealed uric acid, 4 mg, nonprotein nitrogen, 34 mg, and urea, 13 mg. Rapid improvement occurred on a milk diet.

CASE 8—L S, a man, aged 43, had a vesicular eczema which began on the arms one year ago and which spread over the entire body. There was violent itching.

Urinalysis revealed specific gravity, 1.018, a trace of albumin, no casts and numerous pus cells.

Blood examination revealed uric acid, 41, urea, 16, nonprotein nitrogen, 31, sugar, 82. Under a low protein diet and rest, the eruption disappeared.

CASE 9—J S, aged 33, a man, had had generalized pruritus of the body for sixteen years. He weighed 168 pounds (76.2 kg). He was in good health but nervous. Blood examination revealed uric acid, 47 mg, nonprotein nitrogen, 36 mg, urea nitrogen, 16 mg, sugar 47 mg, chlorids, such as sodium chlorid, 497 mg, urine examination specific gravity, 1.029, no albumin or sugar. The blood pressure was 120.

CASE 10—J R, a man, aged 20, had eczema in infancy and was subject to asthma in early childhood. He now had severe eczema of the face, with marked excoriations. Various food allergens were tried, but the results were negative. The patient's general health apparently was excellent. Chemical blood analysis revealed nonprotein nitrogen, 30, urea, 14 mg, sugar, 100, uric acid, 41.

#### INCONSISTENCIES IN BLOOD AND URINARY FINDINGS

The nonprotein nitrogen and urea may be within perfectly normal limits and yet nephritis may be present. A few such cases may be cited.

CASE 11—M S, a woman, aged 25, had a disease which had been diagnosed as lupus erythematosus. She had had nephritis in 1918 and had been confined to a hospital for some months. Examination of the urine showed a specific gravity of 1.010, 16 per cent by volume of albumin, and 50,000 hyaline casts to the ounce of urine. Severe and fatal nephritis occurs in certain cases of lupus erythematosus.

The blood findings were uric acid, 4, nonprotein nitrogen, 35, urea, 16, sugar, 102.

It is here seen that although the patient has a nephritis, the only nitrogenous element in her blood that is abnormal is the uric acid.

CASE 12—E B, a man, aged 59, had recurrent erythematovesicular eczema on the face, arms and legs. He selected his food and ate moderately. The

urine, whereas others<sup>1</sup> do not. These cases represent, we believe, beginning instances of chronic interstitial nephritis.

We have observed, however, other patients in whom the uric acid was high, but in whom the nonprotein nitrogen and urea nitrogen were within normal limits. What is to be said of the hyperuricemia in these cases? The urinalysis in the cases in which examination was made was normal. Brief histories of some of the cases are appended.

In a separate group must be included the cases classified in Table 8. In most of these cases, not only was the uric acid high, but the nonprotein nitrogen and urea were likewise suspiciously above normal limits. These patients in the main represented the age decades from 40 to 70, whereas the previous group contained subjects from 17 to 45 years of age.

TABLE 7—*Findings in a Group of Younger Patients*

Name	Age	Uric Acid	Urea	Non protein Nitrogen	Blood Pressure	Diagnosis	Urine
K B	22	5.4	13	30	130	Eczema	Specific gravity 1.031, no albumin or casts
Miss B	20	4.1	15	31		Intestinal toxemia	
L S	43	4.1	16	31		Eczema	
Mrs K S G	44	4.0	13	34		Eczema	
I P H	39	4.3	16	36		Eczema	
A S	43	4.9	14	30		Eczema	
H C DuB	41	4.8	14	33		Eczema	
J R	20	4.1	14	30		Eczema	
Wm S	17	4.6	18	35		Eczema	
J F F	35	5.0	16	36		Glossitis	
D H	34	4.8	14	30	160	Eczema	
A McL	40	5.5	13	32	135	Eczema	
J S	40	4.3	18	36		Dermatitis herpetiformis	Specific gravity 1.010, no albumin or casts
S H H	45	5.0	18	38		Eczema	

Despite the fact that some of the patients in Table 8 had negative urinary findings, they must be regarded as patients with potential renal dysfunction by reason of the nitrogenous blood values.

With respect to the younger group (Table 7) with high uric acid and low urea and nonprotein nitrogen, scientific conservatism would suggest caution as to any dogmatic interpretation of the hyperuricemia. One might assume that these patients had a gouty or uric acid diathesis, on the other hand, they might be suspected of having some degree of renal incapacity. In beginning disease of the kidney, uric acid is the first nitrogenous constituent to be held back, and, therefore to accumulate in the blood. Later accentuation of renal structural damage would then lead to a decreased elimination of urea and nonprotein nitrogen. May both series of cases not represent merely fine gradations of nephrotic change? Our knowledge of the nature of gout is still involved in obscurity. All observers admit that the kidneys play an

an eczema Some cases as I now refer to sometimes exist off and on for years and are saturated with arsenic and mercurials but which are only relieved by recognizing the complicating item of the free production and circulation of uric acid, and instituting a regime calculated to arrest the continuance of these conditions

Lyman, writing on gout in the "Twentieth Century Practice of Medicine," expresses the following "From the remotest antiquity a connection between gout and certain cutaneous diseases has been remarked by all clinical observers who have seen much of disorders that are experienced by the wealthier classes of society." Furthermore, "Eczema is frequently witnessed among the children of gouty families"

Osler writes "Garrod and others have called special attention to the frequent association of eczema with the gouty habit"

To be sure, what we call eczema is a conglomerate concept that includes many conditions of diverse genesis, which cannot be definitely differentiated on the basis of the cutaneous phenomena alone It would constitute valuable information, if we could scientifically demonstrate some of the dominant causes of eczema The present study suggests that hyperuricemia may be an etiologic factor in the production of many eczematous conditions and allied disorders

We are persuaded to believe that the excess of uric acid in the blood in many of the cases bears a causative relation to the accompanying eczema or allied pruritic disorder, by reason of the frequency of the association of the two conditions among the patients studied by us We are fortified in this belief by the fact that in our experience these cases have responded more favorably and more rapidly to treatment than in previous years when the etiologic factor suggested was not suspected and the patients were not placed on an appropriate dietary regimen

What is the significance of the excess of uric acid in the blood found by us in so large a series of cases?

Leaving out of consideration leukemia and the terminal stage of pneumonia, there are two conditions in which a high blood uric acid occurs—gout and nephritis Without the presence of arthritic manifestations (which were absent in nearly all of our cases) or tophi, it would be hazardous to assert the belief that we were dealing with cases of hemic gout It is quite possible that a considerable proportion of the subjects were suffering from renal change Some unquestionably were, but it would be startling to believe that one half of our patients with eczema—persons who were not "sick" in the ordinary acceptation of the term, and who in the main had no complaint except their cutaneous distress—were nephritic There are, it must be said, a considerable number of cases in which not only the uric acid is pathologically high, but in which the urea and nonprotein nitrogen also are beyond normal limits Some of these patients exhibit albumin and hyaline casts in the

few exceptions, not aware that they were not well except for their cutaneous affections

The uric acid values reported by the foregoing observers were higher than ours, but this may possibly be explained at least in part by a difference of technical methods employed. They state that the blood picture in early interstitial nephritis and in gout are strikingly similar, particularly as regards the increase in uric acid. They suggest that a retention of uric acid may be earlier evidence of renal impairment of an interstitial type than the classical tests of albuminuria and cylinduria.

As early interstitial nephritis and gout present blood findings which are almost similar, the question arises, What are the distinguishing features between the two?

Sir A. B. Garrod,<sup>4</sup> in a postscript to his paper, remarked that it was not his opinion that gout was entirely dependent on the power of the kidney for the excretion of uric acid, he did not think that any hypothesis could be advanced with safety. Von Noorden<sup>5</sup> quotes Garród to the effect that the primary cause of the uric acid retention in gout lies in the kidney. He further says

Levison and Luff showed in a very large series of postmortems in Denmark and England that in cases of interstitial nephritis, uric acid deposits in the articular cartilages are frequently found, although the condition was not suspected during life. Stripped of all unnecessary detail, this means that the retention of uric acid in the blood and the remaining phenomena of gout are the results of primary disease of the kidney. In certain cases, both nephritis and gout are amenable to clinical diagnosis. In other cases, nephritis, and in still other cases the uric acid diathesis remain for a long time, perhaps even up to the end of life, clinically free from symptoms and unrecognized.

He adds

It appears that continuous overloading of the blood with uric acid (nephritis) does not necessarily lead to gout, and, moreover, that this overloading is not followed by uric acid deposition without the accession of another still unknown, specific gouty factor.

Folin,<sup>2</sup> commenting on increased uric acid in the blood in gout and in nephritis, says

The characteristic and extraordinary feature of pure gout is that in most cases only the uric acid is increased. Whether this peculiar fact is to be interpreted in terms of a highly selective activity and correspondingly selective deterioration of the kidneys, or whether it means that uric acid is more difficult to excrete than any other waste product, a possibility suggested by the high normal levels and the excessive variations in the uric acid content of normal bloods, is by no means clear. nor is it certain that either one of these two hypotheses can furnish an adequate explanation. In nephritis leading to true uremia there is a gradual accumulation of all the nitrogenous waste products,

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4 Garrod Sir A. B. Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism and Bright's Disease, *Med. Chir. Trans.* **31** 83, 1848.

5 Von Noorden. *Metabolism and Practical Medicine*, **3** 669, 1907.



important rôle Haig states that it is not excessive production of uric acid but faulty elimination which causes an accumulation

Garrod expresses the same thought when he states that gout depends on a temporary or continuous decrease in the ability of the kidneys to excrete uric acid, by which an overcharging of the blood with this product takes place

Is there in gout a specific incapacity of the kidneys to eliminate uric acid, independent of permanent structural damage?

An interesting commentary on this problem is the observation that in all cases of gout that come to necropsy, the kidneys are found diseased On the other hand, the vast majority of cases of chronic

TABLE 8—*Findings in Patients Between the Ages of 42 and 75*

Name	Age	Uric Acid	Urea	Non protein Nitrogen	Blood Pressure	Urine
D A P	47	4.1	20	43	130	Specific gravity 1.012, no albumin or casts
C B	50	5.3	18	46	115	Specific gravity 1.024, no albumin or casts
Mr A W	42	4.9	20	46	175	Specific gravity 1.018, no albumin or casts
H W H	47	5.9	20	40		Specific gravity 1.019, no albumin or casts
Mrs F C	66	5.8	15	34	185	Specific gravity 1.026, no albumin or casts
Mrs B	48	4.3	11	36		
J K Y	60	4.7	15	31		
H S R	62	4.5	18	37		
Mrs B	55	5.1	20	44		Specific gravity 1.011, trace of albumin, no casts
Dr C	47	4.5	19	42		Specific gravity 1.019, few hyaline casts, no albumin
C S	65	6.2	15	33		Specific gravity 1.012, no albumin or casts, previously had casts for 4 or 5 months
D W C	60	4.2	15	40		
Mr R	75	4.3	13	28		
Mrs G	58	4.7	14	30	150	Specific gravity 1.021, trace of albumin, few hyaline casts
Mrs J M S	62	5.6	15	32	160	Specific gravity 1.011, no albumin or casts
Wm K	42	6.4	16	40	110	Specific gravity 1.032, trace of albumin, many hyaline casts

interstitial nephritis are unaccompanied by symptoms clinically recognizable as gout

Bearing on the interpretation of our cases is the series of cases reported by Myers, Fine and Lough<sup>3</sup>

These writers reported about thirty cases in which there were high uric acid values without a corresponding retention of urea and creatinin, nonprotein nitrogen was not determined Their patients appear, however, to have been hospital cases suffering from other systemic or visceral disorders, whereas ours were patients "on their feet," and, with

<sup>3</sup> Myers, V C, Fine, M S, and Lough, W G The Significance of the Uric Acid, Urea and Creatinin of the Blood in Nephritis, *Int Med* 17 570 (April) 1916

the urease digestion) and ammonium sulphate (resulting from the acid digestion) were added 3 c c of 10 per cent and 3 c c of 40 per cent alkali, respectively, and the liberated ammonia aerated into 5 c c portions of 0.01 normal sulphuric acid. The nitrogen was then determined by titrating the excess of acid with 0.01 normal alkali, the indicator being methyl red containing some methylene blue as a background color. With this indicator, the titration is accurate within 1.5 mg of normal per 100 c c of blood, since a distinct color change is produced with one drop of alkali or acid. Fresh standard acid and alkali solutions were prepared each month. The exact strength of the acid was calculated from the weight of the barium sulphate obtained from 100 c c portions of the acid which were drawn from the same buret used in the subsequent titrations. The alkali, stored in a paraffin lined bottle and protected against the action of carbon dioxide by soda lime, was titrated against the acid before each analysis, and its proper factor obtained. Blank determinations were made with each new lot of reagents.

The precautions necessary in obtaining a filtrate suitable for the uric acid determination have already been pointed out. In our analyses, Benedict's phosphate standard, freshly prepared every six weeks, was employed in preference to the sulphite standard of Folin and Wu, because the more intense blue colors, obtained in the absence of sulphite, permit more accurate colorimetric comparisons. Otherwise the directions outlined by Folin and Wu were strictly adhered to. During the course of our work, several papers were published<sup>8</sup> in which the authors expressed their doubt both as to the accuracy of the uric acid determination and the nonadsorption of uric acid during the precipitation of the proteins. We, therefore, carefully investigated the entire subject and obtained results<sup>9</sup> which show that no adsorption of uric acid takes place if the tungstic acid protein precipitation is carried out as stated above, and that the Folin and Wu procedure for the determination of uric acid yields accurate results.

As a further check on our technic, analyses of normal blood specimens were made throughout the course of the work.

All figures are the averages of at least two closely agreeing results.

*Reagents*—Kahlbaum's urea and uric acid were used, all other chemicals were chemically pure.

*Apparatus*—All comparisons were made in a 5 cm Duboscq colorimeter, by diffused daylight, by the same operator. The latter also determined all zero corrections (maximum error  $< \pm 0.8$  mm). The two 50 c c burets used in the titrations were matched, all pipets were calibrated to deliver

8 Pucher, S. W. (footnote 7), Benedict, S. R., J. Biol. Chem. **51** 187, 1922

9 Brown, H., and Raiziss, G. W., J. Lab. & Clin. Med. **8** 129, 1922

except ammonia, and in such bloods there is no constant relationship between the increase in the uric acid and in that of the total nonprotein nitrogen. But, on the whole, one can say that the uric acid seldom, if ever, shows a greater percentage increase than does the total nitrogen, that the uric acid accumulation, on the contrary, is usually less pronounced. In other words, in cases of generally diminished kidney efficiency one finds no support for the idea that the uric acid retention represents any special difficulty in the process of excretion. The statement made is true at least for advanced cases of nitrogen retention. Whether it is also or equally true for the early stages representing moderate nitrogen retention is not certain. Myers, Krauss and others have drawn the conclusion that the retention and accumulation of the uric acid precedes and exceeds that of the nonprotein nitrogen in the early stages of kidney insufficiency.

Under the circumstances, we would leave the interpretation of the hyperuricemia found in the series of cutaneous diseases studied by us for others to elucidate. We content ourselves with the actual findings which we have presented. A more intensive investigation, which would include the study of the purin metabolism, careful and repeated urinary examinations, blood pressure determinations and renal function tests, would doubtless shed added illumination on the subject.

#### CHEMICAL METHODS EMPLOYED

All blood specimens, both normal and pathologic, were drawn from two to three hours after a light breakfast, and the entire analysis completed on the same day. We found sodium oxalate more advantageous than potassium oxalate as the anticoagulant, owing to its low solubility which precludes the possibility of a large excess of the salt interfering with the subsequent protein precipitation.

The methods of analysis were, generally, those elaborated in 1919 by Folin and Wu.<sup>6</sup>

To 15 cc of whole blood diluted with water to 120 cc in a graduated mixing cylinder, 15 cc of 10 per cent sodium tungstate were added, and the liquid thoroughly mixed. Fifteen cc of two thirds of normal sulphuric acid were then introduced, the cylinder being constantly shaken to prevent any clumping of proteins due to excessive local acidity. After all the acid had been added, the mixture was shaken for a few minutes longer. With this procedure, filtration could be started at once, the filtrates being, invariably, water-clear and neutral to congo red. The importance of having a neutral filtrate from which to precipitate the silver urate as well as the necessity of adding the acid slowly and with constant agitation to prevent absorption of uric acid, has been emphasized by various investigators.<sup>7</sup>

Neither the urea nor the nonprotein nitrogen was determined by nesslerization. To the solutions of ammonium carbonate (obtained by

<sup>6</sup> Folin, O., and Wu, H. *J Biol Chem* **38** 98, 1919.

<sup>7</sup> Folin and Wu (footnote 6), Pucher, S. W. *J Biol Chem* **52** 317, 1922.  
Folin, O. *ibid*, **54** 153, 1922.

TABLE 9—Cases Analyzed—(Continued)

	Name	Age	Sex	Diagnosis	Uric Acid	Non-protein Nitrogen	Urea	Sugar	Crea tin
74	L K	30	M	Eczema	27	36	18	100	13
75	H W	69	M	Eczema	44	39	20	96	15
76	K B	22	M	Eczema	54	20	12	108	12
77	T B	39	M	Eczema	33	40	19	88	12
78	Mrs L	42	F	Eczema	22	30	13	98	11
79	A McL	40	M	Eczema	55	32	13	101	13
80	M E S	40	M	Eczema (mild)	33	41	21	102	15
81	I L B	44	F	Eczema	39	30	14	110	13
82	H T D	51	M	Eczema	33	38	16	106	14
83	T D	19	F	Eczema	20	32	13	106	11
84	H T	40	M	Eczema	33	40	19	118	14
85	E M A	26	F	Eczema	20	38	12	110	12
86	Mrs R	43	F	Eczema	36	34	15	110	12
87	H S	47	F	Eczema (or dermatitis)	23	38	19	101	14
88	M G	23	F	Eczema	18		12		
89	S H H	45	M	Eczema	50	38	18	100	15
90	J J M	42	F	Eczema	24	32	14	102	
91	L R	1	F	Eczema (infantile)	20				
92	S R	32	F	Eczema	27	32	15	93	11
93	C L	45	F	Eczema	33	41	22	104	15
94	E J L	67	M	Eczema (Jan, 1921)	29	53	23	47	28
				(Jan, 1922)	60	38	18	62	17
				(Jan, 1923)	41	30	14	98	
95	B C	47	F	Eczema	33	36	18	116	11
96	J S	42	F	Eczema	30		18		
97	M S	30	F	Eczema	33	41	22	110	15
98	H J H	22	M	Eczema	30	36	18	100	
99	A B	38	M	Eczema and pruritus	40	35	17	102	
100	S H	18	F	Eczema	29	35	17	97	
101	J F K	63	M	Eczema	46	38	19	104	
102	E S	14	F	Eczema	37	36	16		
103	M H S	32	M	Eczema	40	40	21		
104	C W	22	M	Eczema	38	38	19	108	
105	H S	52	F	Eczema	31	38	19	96	
106	S L S	67	M	Eczema	45	37	18	90	
107	H M	31	M	Eczema	54	44	23	100	
108	R J S	59	F	Eczema	40	32	15	115	
109	M S	53	M	Eczema	37	34	16	100	
110	D H F	36	M	Eczema	45	35	16	110	
111	Wm R		M	Eczema	36	35	17	102	
112	Miss M	21	F	Eczema	20		14		
113	J R	20	M	Eczema	41	30	14	100	
114	F B G	21	M	Eczema	29	31	13	92	
115	J G H	40	M	Eczema	41	34	16	95	
116	B F	38	M	Eczema	35	32	16	67	
117	A A	65	M	Eczema (acute erythema)	23	34	16	97	
118	D G	52	M	Eczematoid dermatitis	26	35	12	102	14
119	Mrs R	61	F	Eczematoid dermatitis	23	35	11	112	11
120	E O	42	F	Eczematoid dermatitis	24	39	13	104	14
121	H J	45	F	Eczematoid dermatitis	29	28	13	100	11
122	Mrs P	48	F	Dermatitis	30	31	14	122	13
123	G W T	30	M	Dermatitis herpetiformis	17	39	20	80	15
124	J S	40	M	Dermatitis herpetiformis	43	36	18	98	15
125	F M	70	F	Dermatitis seborrheica	30	40	19	105	15
126	M L B	54	F	Neurodermatitis	31	37	17	98	14
127	P T	31	F	Neurodermatitis	22	30	14	116	11
128	W L B	55	F	Exfoliative dermatitis	54	35	16	144	14
129	N D	60	M	Psoriasis	27	27	13	113	13
130	A O	35	M	Psoriasis	32	25	11	182	16
131	L J	18	M	Psoriasis	25	26	9	65	09
132	M G	44	F	Psoriasis	23	27	9	88	10
					33	27	14	118	11
133	J A H	29	M	Psoriasis	28	29	11	111	15
134	Mrs H	60	F	Psoriasis	45	33	16	90	14
					34	42	18	93	16
135	R S I	55	F	Psoriasis	25	38	18	98	14
136	Mr H	63	M	Psoriasis	52	46	23	88	16
137	Mrs W	45	F	Psoriasis	32	39	14	100	15
138	M D	57	F	Psoriasis	38	38	18	100	12
139	O M C	51	M	Psoriasis	31	31	18	160	12
140	P R		F	Psoriasis	22	32	11	102	
141	E S		M	Psoriasis	42	39	19	107	
142	O O	38	F	Psoriasis	31	30	13	114	
143	O M O	51	M	Psoriasis	36	28	12	147	
144	J K Y	60	M	Parapsoriasis	47	31	15	117	11
145	W M	85	F	Pruritus	18	25	14	110	14

TABLE 9—Cases Analyzed

	Name	Age	Sex	Diagnosis	Uric Acid	Non protein Nitrogen	Urea	Sugar	Creatin
1	Mrs B	48	F	Eczema	43	36	11	106	12
2	Mrs D	66	F	Eczema	58	36	17	119	11
					62	41	21	113	18
3	A B	38	M	Eczema	32	43	17	99	13
					27	36	18	63	12
4	Miss R	18	F	Eczema	37	34	19	107	11
5	R W	57	M	Eczema	63	47	21	80	17
6	L S	43	M	Eczema	41	31	16	82	17
7	Mr H	47	M	Eczema	79	40	20	132	14
				3 months later	49	36	17	110	
8	Mr R	62	M	Eczema	45	37	18	123	14
9	I W	55	F	Eczema	28	28	15	108	13
10	Mr McH	68	M	Eczema	48	46	15	90	15
11	Mrs M	72	F	Eczema	29	41	20	88	16
12	J S S	56	M	Eczema	34	42	15	83	16
13	J S G	44	F	Eczema	40	34	13	81	15
14	Mrs B	55	F	Eczema	51	44	20	95	16
15	Mr F	59	M	Eczema and gout	35	38	15	133	14
16	Mr E	50	M	Eczema	49	45	25	70	15
17	G A B	35	F	Eczema	34	38	15	78	13
18	I F	49	M	Eczema	40	36	21	82	16
19	Mr T	36	M	Eczema	26	42	17	79	15
20	Mrs K	30	F	Eczema	21	35	15	108	15
21	Mr H	60	M	Eczema	63	43	21	114	15
22	Mr B	57	M	Eczema	16	39	19	103	15
23	Mr P	76	M	Eczema	35	40	21	104	14
24	D L	56	M	Eczema	52	52	26	80	17
25	Mr W	42½	M	Eczema	49	46	20	94	15
26	Miss J	20	F	Eczema	29	46	20	96	19
27	Mrs D	22	F	Eczema	22	40	18	80	16
28	Mrs K	30	F	Eczema (acute)	40	46	21	85	14
29	Mrs L	41	F	Eczema	22	29	12	115	11
30	F S C	47	M	Eczema	45	42	19	93	15
31	C S	65	M	Eczema	62	33	15	146	14
32	T B G	70	M	Eczema	70	35		104	197
33	D P	16	F	Eczema	21	37	12	90	16
34	H S R	61	M	Eczema	39	37	18	105	15
35	Mr C	60	M	Eczema	42	40	15	93	14
36	M B F	53	F	Eczema	36	38	19	110	14
37	P H	39	M	Eczema	43	36	16	96	14
38	M E L	61	F	Eczema	26			110	
39	T R	34	F	Eczema	20	36	16	102	12
40	I H D	69	M	Eczema	39	40	19	106	14
41	B H	11	F	Eczema	24	32	14	98	11
42	C K	52	M	Eczema	34	36	15	118	14
43	J G S	57	M	Eczema	25	39	19	121	15
44	S B	45	M	Eczema	31	30	14	96	
45	Mrs B	70	F	Eczema	32	38	20	273	17
46	J M	34	M	Eczema	39	38	17	100	13
47	P R	75	M	Eczema	43	28	13	104	11
48	L C	22	F	Eczema	24	35	14	90	11
49	Mrs S	45	F	Eczema	23	35	16	112	14
50	W B	67	M	Eczema	40	35	15	110	13
51	I H	33	M	Eczema	36	32	13	95	11
52	A S	43	M	Eczema	49	30	14	106	14
53	E B	59	M	Eczema	24	36	16	110	13
54	J S	43	M	Eczema	34	32	13	106	14
55	F O T	48	F	Eczema	24	32	13	100	12
56	L S K	49	M	Eczema	31	33	12	125	13
57	E L S	54½	M	Eczema	38	35	14	110	14
58	R E	18	M	Eczema	31	29	11	90	11
59	J H	60	M	Eczema	38	37	18	94	13
60	H C DuB	41	M	Eczema	48	33	14	90	12
61	J B	42	M	Eczema	36	34	15	98	12
62	D A P	47	M	Eczema	41	43	20	90	14
63	C B	50	M	Eczema	53	46	28	92	18
64	B B	79	F	Eczema	22	39	20	103	13
65	Wm K	42	M	Eczema	64	40	16	86	15
66	Wm S	17	M	Eczema	46	35	18	95	14
67	E C	60	F	Eczema	58	34	15	128	14
68	F G	58	F	Eczema	47	30	14	96	12
69	J M S	62	F	Eczema	56	32	15	130	13
70	A I R	27	M	Eczema	28	30	13	108	14
71	Dr L	52	M	Eczema (mild)	27	54	15	102	15
72	P S	35	F	Eczema	18	39	14	103	11
73	D H	54	M	Eczema	48	30	14	112	13

number of cases including 128 patients, is 3.5 kg which is perfectly normal. The average of the second group, comprising 115 cases, is 4.5, which is abnormal. It would appear, therefore, that there is a definite increase of uric acid with rise in weight, but that beyond 80 kilograms no further rise takes place. This study of 243 patients indicates in general that higher uric acid values are to be expected in heavy persons.

TABLE 10—*Influence of the Weight of the Individual on Uric Acid in Blood*

No. of Cases	Weight of Patient in Kilograms	Average Uric Acid Mg. per 100 c.c. of Blood
8	40-49	2.78
48	50-59	2.83
72	60-69	3.22
66	70-79	4.36
41	80-89	3.75
8	90-99	4.01

#### SUMMARY AND CONCLUSIONS

1 In a chemical study of the blood of over 200 patients suffering from cutaneous diseases, great variations in the uric acid content were found.

2 Over one half of the patients had eczema, and in these an increase in uric acid beyond the maximal normal limit (3.5 mg.) was observed in 50 per cent. of the cases.

3 In some cases of pruritus, both general and local, there were likewise high uric acid figures.

4 Classifying the eczema patients in age decades, it is seen that there is a rising uric acid curve from the fortieth to the seventieth year. This is not evident in the noneczematous subjects.

5 The average uric acid content of the blood in the male subjects was about 25 per cent. higher than among the female patients. The average age of the males was about seven years more than the females.

6 The blood of young patients with eczema did not as a rule contain large amounts of uric acid, but there were some notable exceptions.

7 The cause of the hyperuricemia is a matter for further study, we incline to the view that is to be explained on the basis of renal dysfunction.

8 Patients with psoriasis, acne, urticaria and certain other cutaneous diseases have a lower average uric acid blood content than those suffering from eczema.

9 We believe the hyperuricemia to be etiologically related to eczema and to pruritus in a considerable percentage of the cases studied.

10 Appropriate dietary measures have made many of our patients much more rapidly amenable to treatment than patients previously treated without this therapeutic measure.

TABLE 9—Cases Analyzed—(Continued)

	Name	Age	Sex	Diagnosis	Uric Acid	Non protein Nitrogen	Urea	Sugar	Urea tin
146	W H W	68	M	Pruritus	2.1	32	15	113	12
147	Mr McC	60	M	Pruritus	3.3	37	16	115	14
148	L T	37	F	Pruritus capitis	2.3	26	11	91	14
149	P A	35	M	Pruritus capitis	2.9	29	14	106	14
150	Mrs R	49	F	Pruritus ani	3.1	42	20	94	14
151	H G	38	M	Pruritus ani	6.6	42	21	90	15
152	Mr L	39	M	Pruritus ani	3.5	29	12	102	11
153	J F S	52	M	Pruritus ani et hiemalis	3.1	31	10	66	13
					2.8	39	16	94	13
154	G H B	51	F	Pruritus hiemalis	2.4	38	19	98	13
155	D L	78	M	Pruritus hiemalis	4.7	38	18	99	14
156	F M	30	F	Pruritus ani et vulvae	2.8	36	18	95	18
157	R G	46	F	Pruritus vulvae	2.3	29	13	94	
158	M P W	42	F	Pruritus generalisata	4.0	37	15	82	11
159	F S L	52	M	Pruritus generalisata	4.0	40	19	103	
160	J S	33	M	Pruritus generalisata	4.7	36	16	101	
161	Miss K	24	F	Acne	3.3	34	11	71	14
162	I B	20	F	Acne	2.6		12	103	
163	F H	23	F	Acne	3.1		13	92	
164	W S B	43	M	Acne rosacea	4.6	40	18	118	16
165	R S	30	F	Rosacea	2.4	36	10	121	10
166	L B S	57	M	Rosacea pustulosa	2.7	46	12	123	13
167	B K	38	M	Urticaria	2.8	40	22	70	14
168	I L	57	M	Urticaria	3.9	33	19	91	15
169	Mrs H	48	F	Urticaria	2.6	44	19	97	14
170	Mr W	24	M	Urticaria (acute)	3.0	29	11	110	11
171	A B	35	M	Desluv capillorum	2.5	38	19	102	14
172	H M	35	F	Desluv capillorum	2.2	28	10	110	14
173	Mr K	43	M	Alopecia premature	2.8	34	9	123	12
174	Mr B	61	M	Syphilis	2.8	36	16	116	15
					3.8	38	16	94	14
175	Mrs L	46	F	Syphilis	1.0	35	17	106	11
176	M K	48	M	Syphilis latens	4.4	35	18	93	12
177	M S	25	F	Lupus erythematosus	4.0	35	16	102	15
178	A G	21	F	Lupus erythematosus	3.8	38	19	95	
180	A P	23	M	Xanthoma	1.9	27	12	129	14
					2.6	31	11	134	13
181	Mrs L	44	F	Chloasma	2.3	32	9	108	12
182	Miss B	20	F	Gastro intestinal toxemia	4.4	31	13	76	14
183	F M S	46	M	Keratosis of face	3.1	48	23	119	16
184	Mrs O	47	F	Prurigo nodularis	2.2	35	17	103	12
185	Mrs C	31	F	Gangrene of skin (acute)	2.6	38	17	109	14
186	J E F	35	M	Glossitis exfoliat areata	5.0	36	16	110	14
187	Mr F	72	M	Acute erythematous eruption	3.3	20	15	100	11
188	Mr S	46	M	Ringworm (eczematoid)	2.8	33	15	102	11
189	J H E	35	M	Neurodermatitis	2.8	31	13	126	14
190	Mrs L	55	F	Lingual hemorrhages	2.8		14		
191	Mr J B D	44	M	Folliculitis of neck	3.2	32	15	110	
192	B S	23	F	Fissured fingers	2.1	28	11		
193	M F W	35	M	Psoriasis	4.8	38	19	97	
194	A K		F	Redness and scaling of face	3.2	30	11	101	
195	O R	49	M	Syphilis	4.0	32	15	106	
196	C R	46	F	Syphilis	4.5	47	25	102	
197	Dr C	34	M	Pruritus ani	5.0	30	13	107	
198	C S W	27	M	Pruritus ani	4.1	37	18	103	
199	J J R	46	F	Leukokeratosis of mouth	2.2	38	14	97	

## URIC ACID IN BLOOD

Table 10 shows that the average amount of uric acid in the blood rises from that of the patients weighing between 40 and 49 kilograms progressively up to that of those weighing from 60 to 69 kilograms. A steady increase is noted up to 80 kilograms, but beyond this point no further rise takes place, there being a slight decline in groups of patients of greater weight than 80 kilograms. Although there is a drop in the uric acid content of the blood after the fourth group, the average uric acid value is still above normal limits. The average amount of uric acid in the first three weight groups, comprising a

Exactly one minute after mixing it is centrifuged for fifteen minutes at 1,800 revolutions per minute. The fluid should be at a temperature of approximately 20 C.

Under these conditions, each 0.1 cc of precipitated protein is equivalent to 0.036 gm of protein per 100 cc of fluid.

The actual concentration of protein in 30 specimens of urine were determined by the Kjeldahl method. Widely different concentrations were found, varying from 0.063 gm per 100 cc to 3.01 gm per 100 cc. At the same time, protein determinations were made with our method.

TABLE 2—*Actual Protein Concentration as Determined by Kjeldahl and the Results of Determinations Using the Authors', Purdy's, Strzyzowski's, Esbach's and Tsuchiya's Methods*

Number	Actual Protein Concentration by Kjeldahl Gm per 100 C c	Estimated Concentration Protein Gm per 100 C c				
		Author's Method	Purdy's Method	Strzyzowski's Method	Esbach's Method	Tsuchiya's Method
10	0.063	0.068	0.035	0.042	0.060	0.110
15	0.101	0.108	0.075	0.085	0.080	0.210
9	0.154	0.161	0.102	0.093	0.125	0.200
11	0.166	0.168	0.091	0.116	0.140	0.210
4	0.171	0.157	0.054	0.060	0.075	0.400
5	0.206	0.236	0.105	0.144	0.100	0.300
8	0.213	0.173		0.126	0.130	0.240
23	0.221	0.236	0.089	0.135		2.15
6	0.242	0.271	0.126	0.267	0.280	0.360
14	0.242	0.212	0.094	0.144	0.165	0.470
7	0.282	0.265	0.113	0.178	0.200	0.375
12	0.287	0.330	0.174	0.306	0.210	0.500
1	0.288	0.321	0.130		0.205	0.400
2	0.404	0.374	0.102		0.270	0.510
30	0.448	0.396	0.279	0.314	0.210	2.95
17	0.668	0.706	0.410	0.322	0.500	1.20
26	0.675	0.652	0.400	0.476	0.830	1.05
27	0.691	0.720	0.953	0.476	0.500	1.20
25	1.05	1.238	0.656	0.825	1.35	1.62
3	1.08	1.045	0.153		1.750	0.155
13	1.15	1.17	0.462	0.880	1.02	2.10
29	1.42	1.52	0.593	0.298	1.70	1.75
22	1.48	1.62	1.08	0.140	2.05	5.70
20	1.77	1.83	0.063	0.161	1.70	3.05
16	2.01	1.94	0.855	3.50	1.85	4.10
24	2.01	2.23	1.38	1.700	1.70	3.60
18	2.34	2.30	1.07	2.800	1.75	3.50
19	2.43	2.30	0.212	0.212	1.60	4.10
21	2.89	2.41	2.03	0.199	2.05	4.70
28	3.01	3.10	1.27	1.270	2.55	6.50

and by the clinical methods described by Purdy,<sup>1</sup> Strzyzowski,<sup>2</sup> Esbach<sup>3</sup> and Tsuchiya.<sup>4</sup> These comparisons are given in Table 2.

It will be noted that it is only our method which gives approximately accurate results. In all the others, except Esbach's, there is a considerable constant error, and in all without exception the variable error is larger than in ours. The average percentage error with our method in these thirty determinations is 8.4 per cent with a standard

1 Purdy New York M J 69 844, 1899

2 Strzyzowski Ztschr f Physiol Chem 88 25, 1913

3 Esbach Bull de therap 98 497, 1880

4 Tsuchiya Zentralbl f Med 29 105 1898



# A CLINICAL METHOD FOR THE ESTIMATION OF PROTEIN IN URINE AND OTHER BODY FLUIDS<sup>1</sup>

MARIAN C SHEVKY AND D D STAFFORD, MA  
SAN FRANCISCO

For clinical purposes, none of the methods used in the estimation of protein in urine, plasma, serum, transudates or exudates are satisfactory. Kjeldahl determinations are accurate but require too much time. The various methods given in textbooks on clinical pathology are rapid, but they are also grossly inaccurate. There seems, therefore, to be justification for the description of a centrifuge method which has been used in this laboratory for some time, since it combines simplicity with a considerably greater degree of reliability than any of the clinical methods possess.

The first step in the method is to test the protein containing fluid with heat and acetic acid. If more than a "moderate cloud" is obtained, the fluid should be diluted. This is necessary because the volume of

TABLE 1—*Concentrations of Protein by the Kjeldahl and Authors' Methods*

Qualitative Test Heat and Acetic Acid	Protein Concentra- tion Kjeldahl Gm per 100 C c	Volume of Protein Precipitated, C c
Moderate cloud	0.31	0.85
Light cloud	0.19	0.52
Slight cloud	0.12	0.34
Trace	0.05	0.17
Slight trace	0.03	0.12

precipitated protein should not exceed 1 c c after centrifuging. Since the term "moderate cloud" is vague, we give in Table 1 the concentrations of protein as determined by the Kjeldahl method and the corresponding volumes of protein obtained with our method, for what we call a moderate, light, and slight cloud, as well as the values for the concentrations described as "traces."

The next step is to pipet 8 c c of the fluid, diluted if necessary, into a 15 c c graduated centrifuge tube. Our experience has shown that the ordinary graduated tube is usually quite inaccurate, and we have used tubes which were recalibrated or have ourselves calibrated tubes with long narrow tips.

A layer of 5 c c of Tsuchiya's reagent is allowed to flow over the urine, a stopper inserted and the container slowly inverted three times. Tsuchiya's reagent contains 1.5 gm of phosphotungstic acid and 5 c c of concentrated hydrochloric acid made up to 100 c c, with 95 per cent alcohol.

<sup>1</sup> From the Department of Medicine of Stanford University Medical School.

The only other important variable is the temperature. We have, however, not been able to determine the effect of temperature variations, because when the temperature of an albuminous urine, for instance, is raised or lowered it returns toward room temperature during the centrifuging, so that the degree of temperature which affects the results could be determined exactly only by centrifuging in a room of the required temperature. In the laboratory where the method was developed the room temperature during the day was seldom lower than 18 C or more than 22 C, and within this range temperature variations do not seem to have any appreciable effect.

deviation of  $\pm 97$  per cent. In any series of determinations, 50 per cent should give results which are within  $\pm 65$  per cent of the true value.

The conditions we have selected are, of course, arbitrary, and there is no reason why they should not be altered if they are found inconvenient, so long as a new factor is found by comparison with Kjeldahl results. The time of centrifuging could not be shortened without some, though not a considerable, loss of accuracy. If a speed of 1,800 revolutions per minute cannot be obtained, any constant speed between 1,400

TABLE 3—*The Effect of Varying Speed of Centrifuging on the Volume of the Protein Precipitate*

Revolutions per Minute	Number of Observations	Average Volume of Precipitate, C c
1,400	52	0.495
1,800	50	0.434
2,100	45	0.355
2,300	47	0.301

TABLE 4—*The Effect of Varying Specific Gravity on the Volume of the Protein Precipitate, Time of Centrifuging, Seven Minutes*

Specific Gravity	Revolutions per Minute	Number of Observations	Average Volume of Precipitate, C c
1.005	1,800	4	0.322
1.040	1,800	4	0.318
1.005	2,100	4	0.265
1.040	2,100	4	0.269
1.005	2,300	4	0.254
1.040	2,300	4	0.251

TABLE 5—*Effect of Varying the Length of Time Elapsing Between Adding Tsuchiya's Solution and the Commencement of Centrifuging, Time of Centrifuging, Seven Minutes*

Time in Minutes	Number of Observations	Average Volume of Precipitate, C c
1	8	0.32
2	8	0.33
3	8	0.33
4	8	0.34

and 2,300 revolutions per minute can be chosen and a correction made from the data given in Table 3.

The specific gravity of the fluid containing the protein appears to have no appreciable effect on the volume of the precipitate. The variation in specific gravity was obtained by adding salt to albuminous urine (Table 4).

The time elapsing between the mixing of the fluid and the Tsuchiya's reagent must be kept approximately constant, for it appears that the greater the delay the greater is the volume occupied by the precipitate. Data on this point are given in Table 5.

intake of their patients low. They emphasize the necessity of lowering the level of protein metabolism. More recently, Marsh and Waller<sup>5</sup> showed that the lipemia of diabetes could be diminished in patients who were treated with such diets, and that great increases in fat ingestion were not accompanied by an increase in blood fat.

Up to this time clinicians knew little of the exact quantitative relationships in the metabolism of these substances which are ketogenic to those which are antiketogenic. In a rough way it was realized that "fat burned in the fire of the carbohydrates." In 1914, a most important study was made by Zeller,<sup>6</sup> who maintained a man at a minimal protein metabolism, but varied the proportions of fat and carbohydrate ingested over wide limits. He found that when only one molecule of monosaccharid was present for two molecules of fat in the diet, acetone appeared in the urine. The difficulty in accepting Zeller's results as final lies in the fact that he had no way of measuring the proportions of fat and carbohydrate actually metabolized, and that sources of antiketogenic substances other than carbohydrate were not considered. Nevertheless, Zeller's work marked a definite advance. A similar study made by Ladd and Palmer<sup>7</sup> yielded results agreeing in general with those of Zeller.

Highly important studies of antiketogenesis were carried out by Shaffer,<sup>8</sup> who demonstrated that the oxidation of aceto-acetic acid in alkaline solution by hydrogen peroxid in vitro was greatly accelerated by the simultaneous oxidation of glucose, fructose or glycerol. Shaffer<sup>9</sup> devised a trial method for the calculation of the molecular amounts of ketogenic and antiketogenic substances that might be derived from protein, fat and carbohydrate. This trial method, when applied to data in the literature of starvation experiments, of the Eskimo dietary, and of diabetic acidosis, yielded results which indicated that the minimum molecular ratio of ketogenic to antiketogenic substances for the avoidance of ketonuria in different human subjects was 1:1. A further confirmation of these findings was made by Shaffer<sup>10</sup> by a comparison of the total respiratory quotients with the degree of ketonuria of fasting men and diabetic subjects. He found that a molecular ratio

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5 Marsh, P. L., and Waller, H. G. The Relation Between Ingested Fat and the Lipemia of Diabetes Mellitus, *Arch. Int. Med.* **31**: 63 (Jan.) 1923.

6 Zeller. *Arch. f. Physiol.* 1914, p. 213.

7 Ladd and Palmer. Carbohydrate-Fat Ratio in Relation to the Production of Ketone Bodies in Diabetes Mellitus, *Proc. Soc. Exper. Biol. Med.* **18**: 109, 1921.

8 Shaffer, P. A. Antiketogenesis. I. An in Vitro Analogy, *J. Biol. Chem.* **47**: 433 (July) 1921.

9 Shaffer, P. A. Antiketogenesis. II. The Ketogenic-Antiketogenic Balance in Man, *J. Biol. Chem.* **47**: 449 (July) 1921.

10 Shaffer, P. A. Antiketogenesis. III. Calculation of the Ketogenic Balance from the Respiratory Quotients, *J. Biol. Chem.* **40**: 143 (Nov.) 1921.

# STUDIES OF DIABETES MELLITUS

## II RESULTS OF TREATMENT BY DIET ADJUSTMENT WITH REFERENCE TO MAINTENANCE REQUIREMENT AND THE KETOGENIC-ANTI-KETOGENIC BALANCE<sup>†</sup>

WILLIAM S McCANN, M D , R R HANNON, M D , WILLIAM A PERLZWEIG, PH D , AND EDNA H TOMPKINS, A B  
BALTIMORE

During the years 1921 and 1922 there were two highly important developments of knowledge which promise to be of epoch-making significance in the therapy of diabetes mellitus. The first of these is the regulation of ketogenesis. The second is the specific therapy by means of an extract of the pancreas discovered by Banting<sup>1</sup>.

The problem of treatment of diabetes mellitus has long been in a highly unsatisfactory state. Faced with a disease, which he could not cure, the clinician sought to prolong life by the methods of starvation and undernutrition brought into vogue by Allen,<sup>2</sup> and endorsed by Joslin.<sup>3</sup> Diets were frequently given which furnished adequate amounts of protein, but they were low in carbohydrate content, and generally contained relatively small amounts of fat because of the fear of inducing ketosis by excessive fat ingestion. It seemed generally to have been overlooked that the oxidation of fat continued during starvation and during the use of submaintenance diets, as well as the probability that body fat was capable of giving rise to ketone bodies to the same extent as an equal amount of ingested fat.

A most important contribution was made by Newburgh and Marsh<sup>4</sup> when they called attention to the successful use of high fat diets in the therapy of diabetes. At the time of the introduction of this method, it was generally considered to be a daring procedure. It was shown, however, that ketonuria ceased under the high fat regimen. It became apparent that the amount of fat ingested had little to do with ketogenesis, but that this is influenced by other factors, such as high protein feeding. In their practice, Newburgh and Marsh keep the protein

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\* The Medical Clinic, Johns Hopkins Hospital

1 Banting, Best, Collip, Campbell and Fletcher. Pancreas Extract in the Treatment of Diabetes Mellitus, *Canad M A J* 12 141, 1922

2 Allen, F M, Stillman, E, and Fitz, R. Total Dietary Regulation in the Treatment of Diabetes. Monographs of the Rockefeller Institute for Medical Research, No 11, New York, Rockefeller Institute for Medical Research, Publication Dept

3 Joslin, E P. The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1917

4 Newburgh, L H, and Marsh, P L. The use of a High Fat Diet in the Treatment of Diabetes Mellitus, *Arch Int Med* 26 647 (Dec) 1920

culations on the actual metabolism of the patient as estimated from the data furnished by the basal heat production, urinary nitrogen excretion and the carbohydrate balance. The aim in every case was to furnish a diet which would cover at least the basal energy requirement, with the foodstuffs combined in the proportions advocated by Woodyatt. It was realized that the proportions of foodstuffs actually metabolized would probably be quite different from those of the diet at first, but the

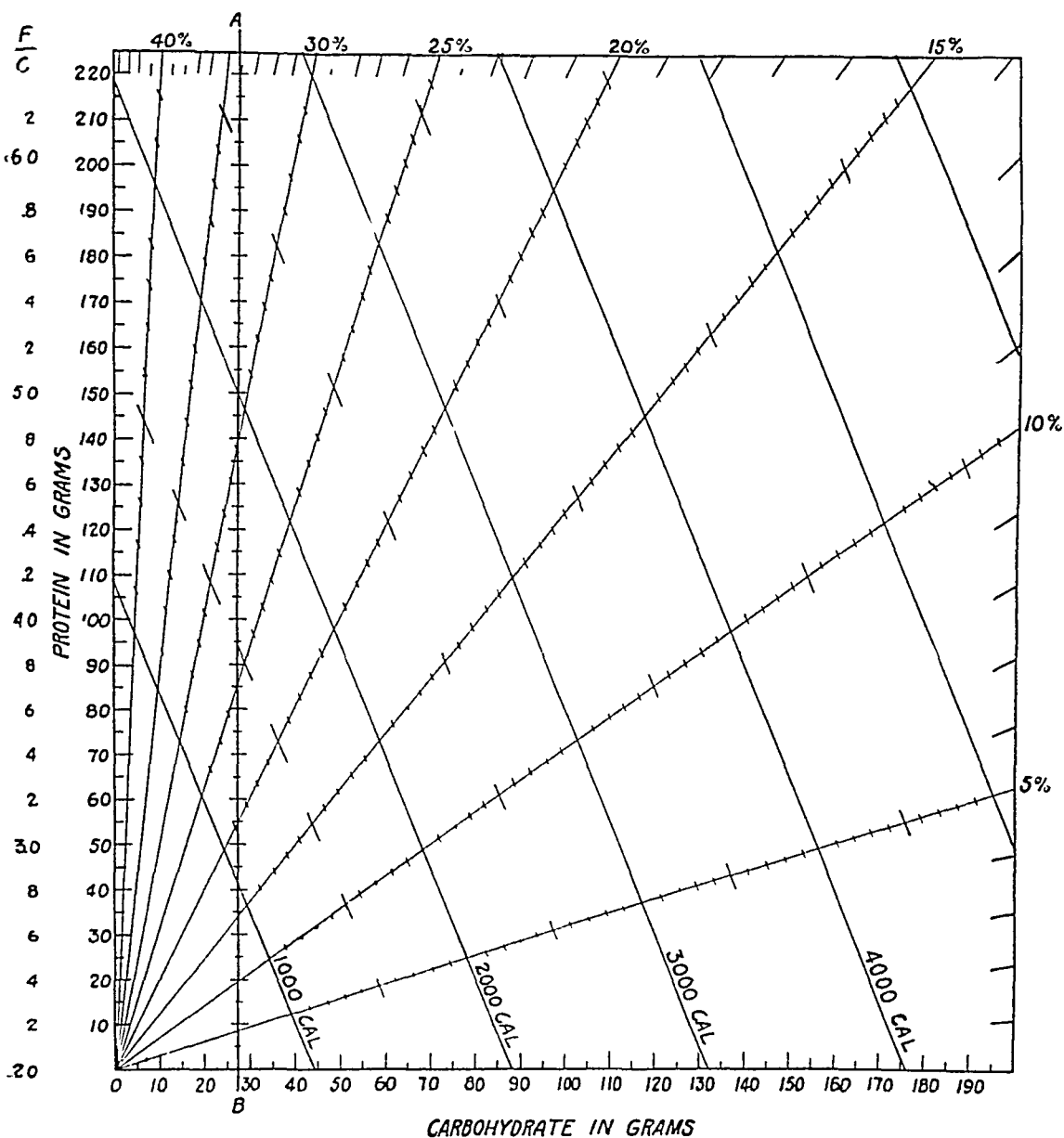


Chart 1—To calculate a diet formula, select the diagonal line representing the number of calories required, choose the radial line corresponding to the percentage of the total calories to be furnished by protein, from the intersection of these two lines read off the amounts of protein and carbohydrate on the axes, the intersection of the  $AB$  with the radial percentage line determines the factor  $F/C$ . This factor multiplied by the number of grams of carbohydrate equals the grams of fat required.

of ketogenic to antiketogenic substances of 1:1 corresponded to a respiratory quotient of 0.76. His analysis of data from various sources indicated that when quotients are higher than 0.76, the catabolism of antiketogenic substances is great enough to remove aceto-acetic acid as fast as it is formed.

More recently, Shaffer<sup>11</sup> has shown that while the 1:1 ratio usually exists at the threshold of ketonuria, when excessive ketogenesis occurs, the amounts of ketone bodies excreted do not correspond with the amount expected if the 1:1 ratio were maintained, but can be explained better if one assumes in such cases the existence of a ratio of two molecules of ketogenic to one molecule of antiketogenic substances. He has, furthermore, tentatively modified somewhat the factors for estimating the molecular amounts of the two classes of substances arising from protein, fat and carbohydrate. With these modified factors, he obtained much better agreement between the predicted and observed excretion of ketone bodies in cases of excessive ketonuria.

Following the appearance of Shaffer's first work, a clear rational statement of the object and method of diet adjustment in diabetes was given by Woodyatt<sup>12</sup>. According to this author, the purpose is to bring the quantity of glucose entering the metabolism from all sources below the quantity which can be utilized without abnormal waste, and to adjust the supply of fat in relation to the quantity of glucose so that freedom from ketonuria may be attained. He proposed a method of combining foodstuffs of a diet in such proportions that for every molecule of diacetic acid which might arise from the foodstuffs of the diet, there should be available from the same sources one molecule of glucose or its equivalent of substances capable of being converted into glucose. These conditions are fulfilled when the foodstuffs are combined in the following proportions:

Fat grams =  $2 \times$  carbohydrate grams plus  $\frac{1}{2}$  protein grams. He described the beneficial results of the use of such a diet in one patient with severe diabetes. From the report of this case, however, it is not possible to determine what actually occurred in the patient's metabolism because the urine nitrogen and the basal heat production were not determined.

The method of diet adjustment advocated by Woodyatt seemed so rational that it was introduced into the practice of this medical clinic. It was felt from the outset that it was highly essential to base all cal-

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11 Shaffer, P. A. Antiketogenesis. IV. The Ketogenic-Antiketogenic Balance in Man and Its Significance in Diabetes, *J. Biol. Chem.* **54**: 399 (Oct.) 1922.

12 Woodyatt, R. T. The Object and Methods of Diet Adjustment in Diabetes Mellitus, *Arch. Int. Med.* **28**: 125 (July) 1921.

at Bellevue Hospital. Feces and urine collections, diet preparation and calculations were carried out in a manner identical with that described by these authors.

Nitrogen determinations on feces and urine were made by the Kjeldahl method. Phosphorus was determined gravimetrically by an official method.<sup>15</sup> Calcium determinations were made by McCrudden's method.<sup>16</sup> The urine sugar was usually determined by titration with Benedict's copper reagent. When present in amounts insufficient to give a qualitative test with copper reagents, the total urine sugar was determined by Benedict's colorimetric method.<sup>17</sup> In certain of the cases the total acetone bodies were determined by the method of Van Slyke and Cullen,<sup>18</sup> and reported as beta-hydroxybutyric acid. In other cases, the total organic acid excretion was measured by the method of Van Slyke and Palmer.<sup>19</sup> Except in well-marked ketonuria, the acetone bodies make up only a part of the total organic acids. Ammonia was determined by the method of Van Slyke and Cullen.<sup>20</sup>

The analyses of blood for sugar and carbon dioxide combining power were made on specimens collected before breakfast. The sugar of the whole blood was determined by the method of Folin and Wu.<sup>21</sup> For the determination of the alkaline reserve of the plasma, Van Slyke and Cullen's method was used.<sup>22</sup>

Many of the basal metabolism determinations were made in the course of respiration experiments with the Tissot spirometers, Loven valves and an analyzers, as described in a previous publication.<sup>23</sup> For other patients, the routine procedure was to determine the metabolism in a closed circuit apparatus,<sup>24</sup> equipped with a graphic recording

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15 Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, Washington D. C., 1920, p. 2

16 McCrudden, F. H. The Determination of Calcium in the Urine, *J. Biol. Chem.* **10** 187, 1911-1912

17 Benedict, S. R., and Osterberg, E. A Method for the Determination of Sugar in Normal Urine, *J. Biol. Chem.* **48** 51, 1921

18 Van Slyke, D. D., and Cullen, G. E. Studies in Acidosis. VII The Determination of Beta-Hydroxybutyric Acid, Acetoacetic Acid, and Acetone in the Urine, *J. Biol. Chem.* **32** 455, 1917

19 Van Slyke, D. D., and Palmer, W. W. Studies in Acidosis. XVI The Titration of Organic Acids in the Urine, *J. Biol. Chem.* **41** 567, 1920

20 Van Slyke, D. D., and Cullen, G. E. A Permanent Preparation of Uricase and Its Use in the Determination of Urea, *J. Biol. Chem.* **19** 211, 1914

21 Folin, O., and Wu, H. A. A Simplified and Improved Method for the Determination of the Sugar in the Blood, *J. Biol. Chem.* **41** 367, 1920

22 Van Slyke, D. D., and Cullen, G. E. The Bicarbonate Concentration of the Blood Plasma and a Method for Its Determination, *J. Biol. Chem.* **30** 289 and 347, 1917

23 McCann, W. S., and Hannon, R. R. Studies of Diabetes Mellitus. I The Effect on the Respiratory Exchange of the Ingestion of Glucose, Glycerol, Calcium, Hexose Phosphate, Calcium Glycerophosphate, *Bull. Johns Hopkins Hosp.* **34** 73 (March) 1923

24 Metabolor made by the Toledo Technical Appliance Co.



hope was that the metabolism would gradually adapt itself to these proportions. Certain variations from Woodyatt's procedure were introduced, namely, in regard to the protein of the diet. This, it was felt, should be kept low in order to facilitate the diminution of the patient's protein metabolism. After reaching a minimal protein metabolism, the protein of the diet was increased to cover the requirement. This general plan of treatment was outlined in a previous communication,<sup>13</sup> together with a chart for the rapid calculation of the diet formula. This chart has been so useful that it has been reproduced in Figure 1.

The equimolecular ratio of ketogenic to antiketogenic substances was adhered to in spite of the later work of Shaffer<sup>11</sup> and others, which tended to show that this ratio furnished more carbohydrate than was necessary for the avoidance of ketone formation. As Shaffer himself pointed out, the molecular ratio is almost always 1:1 at the threshold of ketonuria, and this ratio is certainly the only safe minimum for clinical use.

Although the general plan of treatment was based on the idea of giving every patient at least enough food to cover the basal energy requirement (basal metabolism plus 10 per cent), it was anticipated that a small percentage of patients would be unable to take this amount of energy in such diets without glycosuria. For such patients, some additional means of therapy, such as the use of insulin, is imperative.

Through the kindness of Dr. G. H. A. Clowes of the Eli Lilly Research Laboratories, it has been our privilege to study the effects of "insulin" (Iletin) on diabetic patients. One of the objects of this report on the dietotherapy alone is to afford some typical controls for a subsequent report of the use of dietotherapy plus insulin therapy.

During the year following the beginning of the present study, approximately 100 patients were treated in the manner to be described. Many of these patients were in general wards, especially in the female and negro wards, in which the most accurate excreta collections were impossible, and in which occasionally extra food was taken. The subjects of the present report were all studied in the white male ward of the medical clinic, which is equipped with a metabolism room with its own special diet kitchen. The observations of these patients were all made with the highest degree of accuracy.

#### METHODS OF STUDY

The management of the metabolism ward is essentially that described by Gephart and DuBois<sup>14</sup> for the ward of the Russell Sage Institute.

13 Hannon, R. R., and McCann, William S. A Graphic Method for the Calculation of Diabetic Diets in the Proper Ketogenic Antiketogenic Ratio, *Johns Hopkins Hosp. Bull.* **33**: 128 (April) 1922.

14 Gephart, F. C., and DuBois, E. F. The Organization of a Small Metabolism Ward, *Arch. Int. Med.* **15**: 829 (May) 1915.

TABLE 1—*Diet and Metabolism in Case 1*

Date	Urine					Blood		Diet		Foodstuffs Metabolized						Food, Calories	Calories Required Estimated	Body Wt., Kg	Surface Area, Sq M		
	Volume, Cc	Sugar, Gm	Acetone	Diabetic Acid	Total Organic Acid, Cc N/10	Nitrogen, Gm	Carbon Dioxide, C P Volume, %	Sugar, %	Protein, Gm	Fat, Gm	Carbohydrate, Gm	Protein, Gm	Fat, Gm	Carbohydrate, Gm	Available					F A G	
															Gm						Gm
12/15/21	2,900	56.3	+++	+++		18.6	27.7	0.351	20.6	110	50.7	111	126	-56	21	162	7.7	1,400	44.4	1.49	
12/16/21	3,150	72.5	+++	+++		19.8	30.2	0.303	20.8	112	50.2	123	106	-22	60	152	2.6	1,314			
12/17/21	6,110	92.6	+++	+++		25.1			20.4	111	51.6	157	100	-42	59	162	2.7	1,331			
12/18/21	5,170	106.5	+++	+++		20.2	37.4	0.272	20.4	111	51.6	125	120	-55	30	165	5.5	1,286			
12/19/21	5,370	97.8	+++	+++		18.2			19.5	109	51.2	114	121	-47	31	161	5.2	1,307			
12/20/21	3,600	49.3	+++	+++		19.1	53.7	0.268	0	0	0	119	120	-49	32	163	5.1	0			
12/21/21	4,330	50.2	+++	+++		19.1	58.8	0.234	0	0	0	119	98	0	79	143	1.8	200			
12/22/21	5,090	28.0	++	++		15.9			61.2	110	26.1	99	106	2	70	141	2.0	1,350			
12/23/21	5,950	119.0	++	++		14.9	65.5	0.356	60.2	109	40.4	93	?	?				1,424			
12/24/21	6,200	100.4	++	++		12.4			17.5	111	51.8	78	?	?				1,312			
12/25/21	5,160	47.5	++	++		9.3	66.2	0.290	15.2	110	52.2	58	133	5.3	52	146	2.8	1,400			
12/26/21	6,170	30.6	++	++		11.1			58	112	50.0	69	112	19.4	71	130	1.8	200			
12/27/21	4,820	25.4	++	++		10.6			66	110	50.7	66	110	25.3	75	127	1.7	1,338	45.8		
12/28/21	6,160	44.0	++	++		15.4			96	?	?	?	?	?				1,332			
12/29/21	5,720	10.4	++	++		10.5			20.9	110	50.4	66	104	40.1	89	121	1.4	1,337			
12/30/21	4,300	35.1	++	++		8.2		0.158	21.6	110	51.4	51	121	16.3	58	130	2.2	1,311			
12/31/21	5,000	28.7	++	++		8.5			19.7	110	49.3	51	118	20.6	63	128	2.0	1,304			
1/1/22	4,720	36.3	++	++		9.9	68.5	0.294	41.5	115	46.3	62	119	10.0	58	133	2.3	1,429			
1/2/22	4,470	37.2	++	++	634	10.8			41.5	115	46.3	67	117	9.1	60	133	2.2	1,429			
1/3/22	4,660	32.5	++	++	457	11.9			42.0	114	47.0	74	106	14.5	68	126	1.8	1,425			
1/4/22	4,500	10.7	++	++	431	9.0			41.0	116	46.5	55	110	35.8	79	122	1.5	1,434			
1/5/22	6,300	0	++	++	431	6.9			17.4	112	44.1	43	112	44.1	80	119	1.5	276			
1/6/22	4,550	0	++	++	465	5.9			12.9	118	38.2	37	117	38.2	71	121	1.7	178			
1/7/22	3,850	0	++	++	487	7.7			41.9	115	46.2	48	109	46.2	85	118	1.4	1,438			
1/8/22	3,560	0	++	++	527	6.1		0.156	41.6	116	46.7	38	118	43.4	77	122	1.6	1,428			
1/9/22	2,250	0	++	++	666	6.0			49.5	121	40.8	38	127	43.5	78	131	1.7	1,515			
1/10/22																			1.48	1.51	

device so that the principle of Krogh<sup>25</sup> was used in the measurement of the oxygen consumed, assuming an average respiratory quotient of 0.72 in calculating heat production of diabetic subjects

Calculations of the ketogenic-antiketogenic balance have been based on the actual metabolism of the patients, but only in cases in which the subjects were kept quietly in bed so that the heat production could be estimated (basal metabolism plus 10 per cent) For this reason, the rule was made that patients showing ketonuria should be kept in bed as nearly at absolute rest as possible until the urine ceased to contain acetone In calculating the foodstuffs metabolized, the following procedure was followed

$$\begin{aligned} \text{Urine Nitrogen grams} \times 6.25 &= \text{Protein metabolized, gm P} \\ \text{C, carbohydrate utilized} &= \text{Food carbohydrate minus urine sugar} \\ \text{Fat oxidized, grams} &= \frac{\text{Total heat produced} - 41(P + C)}{9.3} \end{aligned}$$

Total heat produced = Basal metabolism plus 10 per cent

In the diet and metabolism tables the available diacetic acid, *FA*, and the available glucose, *G*, were calculated by the method of Wood-yatt,<sup>12</sup> in accordance with the formulas

$$\begin{aligned} FA &= 0.9F + 0.46P \\ G &= 0.1F + 0.58 + C \end{aligned}$$

in which *F* = grams of fat, *P* = grams of protein, and *C* = grams of carbohydrate

The diet and metabolism tables have been abbreviated by deleting relatively unimportant parts for the sake of space The essential data from the complete tables is recorded graphically All data relative to ketogenic-antiketogenic balance during periods of significant ketonuria have been retained in the tables

#### REPORT OF CASES

CASE 1—*History*—W. A., a mechanic, aged 22 years, admitted to the hospital on Dec. 15, 1921, complaining of general weakness, had been in good health until October, 1921, when he noticed excessive thirst, hunger, frequent and excessive urination, general weakness and a loss of weight of 20 pounds (9.07 kg) in two months For three weeks before admission he had noticed that he was drowsy and that he tired easily For two weeks he had suffered from a dry cough accompanied by a choking sensation Drowsiness had increased very much in the two days prior to admission

The family history was not important except for the fact that his father was very obese The past history was unimportant His best weight was 145 pounds (65.77 kg) One year before admission, he weighed 140 pounds (63.5 kg) and maintained this weight up to the onset of illness His weight on admission was 102 pounds (46.26 kg)

<sup>25</sup> Krogh, A. Respiration Apparatus for the Determination of the Energy Metabolism in Man, *Wien klin Wchnschr* 35:290, 1922

almost as much carbohydrate as before. At this time glycosuria ceased. Between January 8 and 15, it was possible to increase the calories to 1,500 gm and the protein intake to 50 gm, without a return of glycosuria. This diet was continued up to January 30, with the exception of January 15, on which day green vegetables were given.

In Period I, from January 18 to 22, inclusive, stools were saved quantitatively, separation of feces being accomplished by means of carmine given with the breakfast of the first day of each period. Periods II, III, and IV began on January 23 and 28 and on February 2, respectively. Complete excreta collections were made for the purpose of determining the balance between the intake

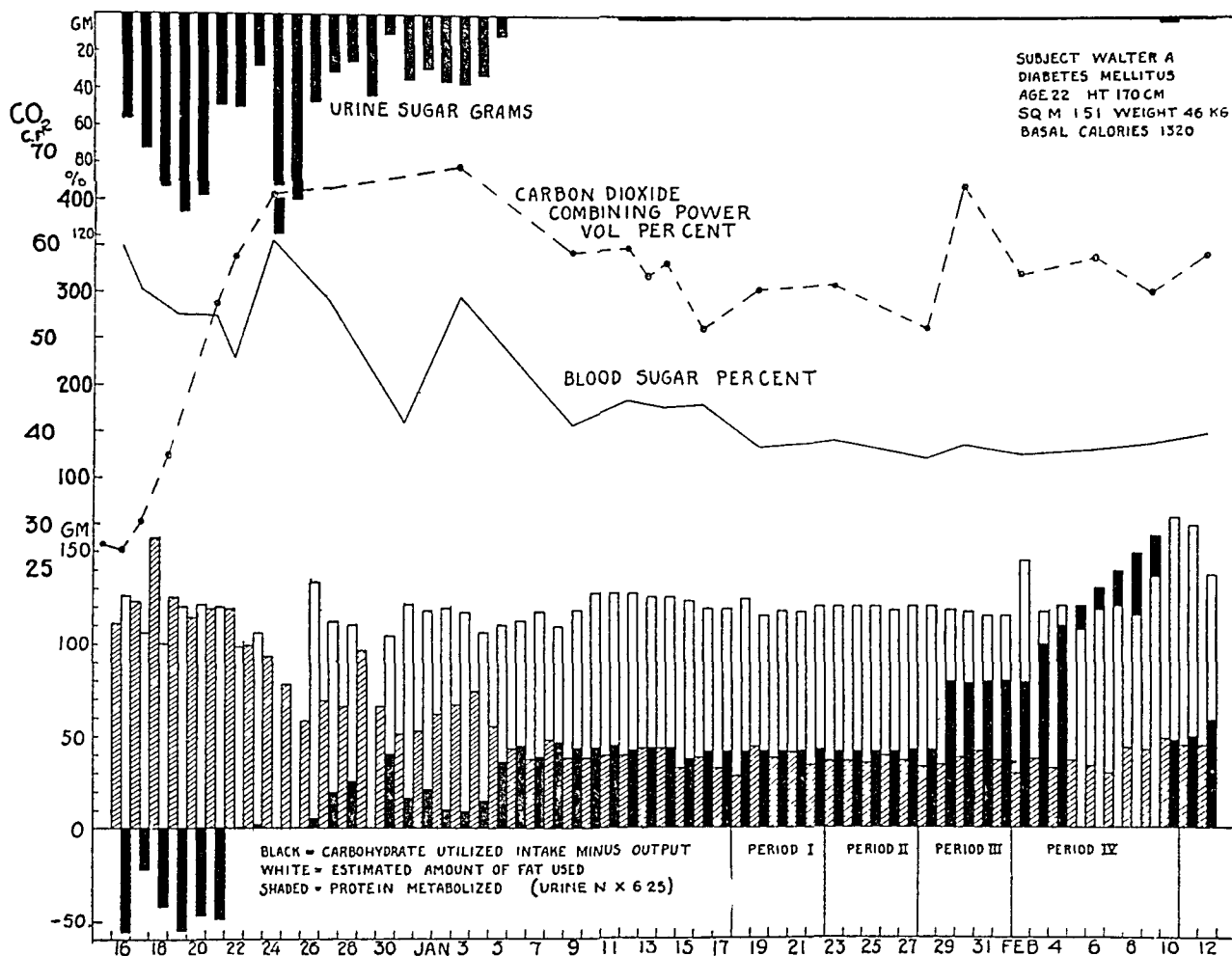


Chart 2 (Case 1)—Metabolism chart of Walter A. Black columns represent carbohydrate in grams utilized or excreted in the urine. The shaded columns represent protein metabolism in grams per diem. Unshaded columns represent the estimate of the amount of fat oxidized a day.

and outgo of calcium, phosphorus and nitrogen. These results will be discussed separately (Table 2).

During Period II, 60 gm of calcium hexose phosphate were given daily. Though this increased the available carbohydrate by 37 gm, no increase in blood sugar or sugar excretion occurred.

During Period III, it was demonstrated that the patient could tolerate the addition of 375 gm of glucose to the diet just as well. At the time it was thought that the accumulation of a large phosphorus balance during Period II

*Physical Examination*—Examination on Dec 15, 1921, revealed a temperature of 97 F, pulse rate, 94, respirations, 24, blood pressure systolic, 115, diastolic, 78, height, 170 cm. The patient was a markedly emaciated young white man, lying quietly in bed and apparently very drowsy, the respiratory rate and amplitude were both increased. A fruity odor was noticeable. When aroused the patient was mentally clear but soon lapsed into drowsiness. The face was flushed and dry. The cheeks were sunken. The mucous membranes were red, the tongue beefy, dry and furrowed. The eyes were normal, except for low ocular tension. No other abnormalities were noted except a slight impairment of resonance and a few moist râles in the left upper side of the chest. This observation was not confirmed on subsequent examination. The urine showed the presence of a large amount of sugar, acetone and diacetic acid. The blood flowed sluggishly, it was rather thick and dark red. The carbon dioxide combining power of plasma was 27.7 volume per cent. There were 6,400,000 red blood cells, 18,000 white blood cells and 90 per cent hemoglobin. The Wassermann reaction was negative. The patient was starved and forced to take large amounts of water.

*December 16* The patient was less drowsy. The odor of acetone persisted. Evidence of desiccation was still marked. Starvation was continued. During this day the fluid intake exceeded the output by 3,000 c.c. The hyperpnea tended to diminish.

*December 17* The patient was more alert in the morning. He was given 21 gm of protein, 110 gm of fat and 51 gm. of carbohydrate. The blood plasma taken in the morning showed the same low carbon dioxide combining power, and a marked hyperglycemia, 0.351 per cent. Further data are given on the metabolism chart.

*December 18* Steady improvement was noted, the patient was brighter and more comfortable.

*December 19* Hyperpnea and odor of acetone were much diminished. Roentgen-ray report. Chest. The lungs were clear.

*December 24* The patient's condition was definitely improved.

*January 4, 1922* The patient admitted having stolen food on one occasion, December 29. On January 5, he was admitted to the special metabolism ward.

*Comment*—The course of the patient under treatment can best be followed by reference to the diet and metabolism chart in Table 1. Much of the data is recorded graphically in Chart 2.

The diet from December 16 to 20 furnished enough calories to cover the basal metabolism. In this period, the evidences of acidosis disappeared, the carbon dioxide capacity of the plasma increased, and hyperglycemia was somewhat less. Large amounts of sugar continued to be excreted.

In order to hasten the disappearance of glycosuria, the patient was starved again on December 21, and given only 1,000 gm of 5 per cent vegetables on December 22. This was partly effective in reducing both the blood sugar level and glycosuria.

On December 23 and 24, the diet furnished about 1,400 calories, of which 19 per cent were derived from protein, fat and carbohydrate, being in the proportions of Woodyatt's formula. This was thought to be too much protein, because on the second day the blood sugar had increased, and glycosuria was greater.

On the twenty-fifth and twenty-sixth, the diet was again changed to give about 1,300 calories, with 5 per cent derived from protein. This was followed by a decreased sugar elimination. On the twenty-seventh, only 1,000 gm of green vegetables were given, and from the twenty-eighth to January 1 inclusive, the 1,300 calorie diet was resumed. During this period a break in diet was admitted.

From January 2 to 5 the amount of protein given was doubled. On the sixth and seventh the diet was low in protein, contained almost no fat, but

might have had a favorable effect on the carbohydrate tolerance. That this was probably not the case became apparent later when other patients were observed to show similar increases in carbohydrate utilization on a similar dietary regimen to which phosphorous compounds were not added.

During Period IV, the carbohydrate intake was slowly increased to 160 gm without any increase in blood sugar level or in glycosuria. It was considered unwise to continue this increase. That this probably represented the maximum diet which could be tolerated was shown by the fact that on February 10 the sugar excretion rose slightly.

The patient, having been trained to weigh and calculate the composition of his diets accurately, was permitted to leave the hospital on Feb 13, 1922, to return to work. He was advised to keep his diet within the limits of the diets given on February 11 and 12, allowing him between 1,700 and 1,950 calories. He remained well—the urine being practically sugar free—and at work during the spring and summer following his discharge. He adhered to his diet for a period of six months, after which he ate anything he desired. On Oct 10, 1922, he caught cold and became ill and weak. He sought treatment from a chiropractor, who prescribed a liberal carbohydrate diet in addition to his manipulations. He was obliged to quit work on October 19. His ankles became much swollen. He returned to Johns Hopkins Hospital for further treatment on Nov 2, 1922.

*Second Admission*—Examination showed practically the same findings as on the previous admission, except that the clinical evidences of acidosis were not so marked. The tendon reflexes in both upper and lower extremities could not be elicited. There were 4,664,000 red blood cells, 9,666 white blood cells and 75 per cent hemoglobin. An incomplete twenty-four hour specimen showed the presence of more than 200 gm of sugar and large amounts of acetone and diacetic acid. Roentgen-ray examination of the lungs showed no abnormality.

The patient's progress under treatment can best be followed by reference to the diet and metabolism chart, Table 3, which is graphically represented in Chart 3.

On a diet slightly above the theoretical requirement, there was a rapid development of acidosis, as shown by the rapid fall in carbon dioxid combining power of the blood plasma.

The progress of the acidosis was arrested by substitution of glycerol for carbohydrate in the diet on November 7 and 8, 36 gm of glycerol being added to 40 per cent cream. The carbon dioxid combining power rose and continued rising on the subsequent days on which the patient received a submaintenance diet containing only 11 gm of protein.

From November 7 to 15, quantitative estimation of the excretion of acetone bodies was made. These bodies were calculated as beta-oxybutyric acid. The excretion decreased from 38 gm on November 6 to 5 gm on November 9, during which time the carbon dioxid capacity of the blood plasma increased from 29.6 to 47.8 volume per cent. Acetone excretion diminished to 0.69 gm on November 15, and qualitative tests were negative between the fifteenth and seventeenth, at which time the FA/G ratio was between 1.85 and 2.00. There is a striking parallelism between the amounts of beta-oxybutyric acid excreted and the FA/G ratios, which is brought out graphically in Chart 4 (see also Tables 3 and 4).

A submaintenance diet, 1,240 calories, was continued until November 29. The protein of the diet was kept low, between 11 and 22 gm. The protein metabolism decreased rapidly, but the patient remained in negative nitrogen balance. The sugar excretion decreased slowly until qualitative tests were negative on November 25. The patient gained in weight during this period in which he was receiving insufficient food to cover either energy or protein requirement. This increase in weight is probably due to water accumulation. Slight facial edema was sometimes noticeable.

The blood sugar did not reach normal limits until November 30. Between November 29 and December 8, there was a rather rapid increase in both

TABLE 2—Nitrogen, Phosphorus and Calcium Balances in Case 1

Period	Dates Inclusive	Food N, Gm	Urine N, Gm	Feces N, Gm	Total N Excreted, Gm	N Balance, Gm	Food P, Gm	Added P, Gm	Total P In take, Gm	Urine P, Gm	Feces P, Gm	Total P Excreted, Gm	P Balance, Gm	Food Ca, Gm	Added Ca, Gm	Total Ca In take, Gm	Urine Ca, Gm	Feces Ca, Gm	Total Ca Excreted, Gm	Ca Balance, Gm
I	Jan 18-22	40.5	101.7	13.95	115.7	-75.2	13.08	0	13.08	4.15	8.15	12.30	+0.78	3.17	0	3.17	1.70	2.81	3.51	-0.34
II*	Jan 23-27	40.5	63.6	17.27	80.9	-40.4	13.06	6.88	69.91	9.86	48.10	57.96	+11.08	3.17	71.67	74.84	1.55	58.39	59.94	+14.91
III	Jan 28-Feb 1	40.0	53.2	15.97	69.2	-29.2	13.03	0	13.03	3.75	10.12	14.17	-1.11	3.20	0	3.20	1.06	7.08	7.74	-1.58
IV	Feb 2-11	75.2	80.4	35.41	115.8	-40.6	27.11	13.19	40.30	8.52	28.61	37.13	+3.17	7.28	17.11	21.42	1.99	21.91	26.90	-2.48

\* Calcium hexose phosphate, 300 gm

TABLE 3—Diet and Metabolism Data in Case 1, Second Admission

Date	Urine				Blood		Diet Received			Foodstuffs Metabolized				Food Calories	Calculated Requirement	Body Wt., Kg	Surface Area, Sq M
	Volume, Cc	Sugar, Gm	Acetone	Diacetic Acid	Butyric Acid, Gm	Total Nitrogen, Gm	Carbon Dioxide, Vol %	Sugar, %	Protein, Gm	Fat, Gm	Carbohydrate, Gm	Valuable F.A., Gm	Avail G, Gm				
11/ 3/22	3,940	204.8	+++	++		3.1	17.5	0.237	39.7	128	56.1	153	22.9	1,382	1,400	46.5	1.52
11/ 4/22	2,380	90.0	+++	++		11.9	28.1	0.250	39.9	129	57.0	153	14.8	1,590	1,400	46.5	
11/ 5/22	3,300	91.0	+++	++		10.3	29.6	0.235	41.9	131	53.5	153	13.0	1,605	1,400		
11/ 6/22	6,450	90.0	+++	++		9.9	31.5	0.231	7.8	138	108	142	30.0	1,370	1,400		
11/ 7/22*	6,450	54.0	++	+		9.5	31.7	0.234	7.8	127	108	130	50.2	1,370	1,400		
11/ 8/22*	4,400	31.0	++	+		6.1	34.7	0.231	10.4	125	15.8	129	16.2	1,370	1,400	43.3	
11/ 9/22	3,420	20.0	++	+		4.3	17.8	0.231	10.4	130	17.9	129	16.2	1,370	1,400	42.1	
11/10/22†	3,420	62.4	+	—		4.3			26.6	114	13.4	142	16.3	1,382	1,400		
11/11/22	3,540	51.0	+	—		6.5			26.6	114	13.4	142	16.3	1,382	1,400		
11/12/22	3,760	37.5	+	—		5.4			40.4	113	2.6	147	35.1	1,042	1,400	43.7	1.48
11/13/22	3,900	33.5	+	—		5.3			33.8	120	11.6	132	43.7	1,035	1,400	45.0	
11/14/22	3,500	22.5	+	—		4.6			33.1	128	15.1	130	47.1	1,036	1,400	46.0	
11/15/22	3,520	14.4	+	—		4.4			28.5	127	23.2	127	52.1	1,041	1,400	46.0	
11/16/22	3,840	11.5	—	—		4.7			27.6	123	31.0	123	62.2	1,041	1,400	48.0	
11/17/22	3,750	13.5	—	—		4.5			120	120	36.5	121	65.4	1,040	1,400		
11/18/22†	3,700	11.8	—	—		1.9			27.8	123	33.0	124	61.0	1,215	1,400	49.0	

\* Added glycerin 36 gm to 40 per cent cream

† Resp expt 30 gm glucose

‡ Patient up Total calories required unknown

The basal heat production and respiratory quotients obtained on different occasions are given in Table 5

CASE 2—*History*—Samuel P, was admitted on Jan 31, 1922, complaining of diabetes. The patient first noticed polyuria, polydipsia and polyphagia in September, 1921. He frequently passed "a gallon of urine a night." His condition became much worse about Christmas, 1921, at which time he was first given dietary treatment by a physician. His symptoms diminished, so that at the time of admission there was no nocturia.

His mother, maternal aunt and maternal grandmother all had diabetes. The family history otherwise was unimportant.

The patient enjoyed excellent health until September, 1921. In 1917, the vision of the right eye was partially destroyed by an electric flash. In the same year, he had a single soft sore on the penis, at the base of the prepuce, which

TABLE 4—*Ketogenesis in Case 1*

Date	Foodstuffs Metabolized			Total Acetone Bodies Excreted, Gm	Excess Ketogens Millimols L	Ketogens Total Millimols K	Ketogens Oxidized Millimols K—E=K'	Anti ketogens Millimols A	Ratio K A	Ratio K' A
	Protein, Gm	Fat, Gm	Carbohydrate, Gm							
11/ 6/22	61.5	138	—36.0	57.4	551	618	67	74	8.4	0.9
11/ 7/22	59.4	127	—7.2	36.7	353	578	225	223	2.6	1.0
11/ 8/22	37.8	125	15.8	19.5	188	521	333	281	1.9	1.2
11/ 9/22	26.6	130	17.9	7.8	75	511	436	260	2.0	1.7
11/10/22	26.6	144	—13.4	12.9	124	559	435	94	5.9	4.6
Av 9 and 10					100	535	435	177	3.0	2.5
11/11/22	40.4	143	—2.6	3.1	30	589	559	197	3.0	2.8
11/12/22	33.8	129	11.6	3.0	29	524	495	247	2.1	2.0
11/13/22	33.1	128	15.1	3.5	34	520	486	263	2.0	1.8
11/14/22	28.5	127	23.2	1.1	10	504	494	293	1.7	1.7

TABLE 5—*Basal Heat Production and Respiratory Quotients*

	Basal Metabolism, Calories per Hour	Respiratory Quotient
Jan 25, 1922	54.9	0.77
Jan 29, 1922	62.2	0.75
Feb 8, 1922	60.8	0.82
Nov 10, 1922	54.8	0.70
Dec 22, 1922	65.6	0.76

was treated locally by cauterization. Six weeks later there was a rash which covered his back and chest. One year later, the blood Wassermann reaction was reported positive. He received eight intravenous injections of arsphenamin, and seventy-two injections of mercury into the buttocks. The patient said that he had always been nervous, easily excited, that he drank heavily and smoked excessively. He had always done hard work on a farm. His best weight was 174 pounds (78.9 kg) in 1919. On admission, he weighed 65 kg (144 pounds).

*Physical Examination*—Temperature, pulse and respiration were normal. The patient's height was 175 cm, and he weighed 65 kg. He was a well developed, somewhat undernourished young white man, lying quietly and comfortably in bed. Respirations were normal in rate and amplitude. There was no odor of acetone on the breath. Over the skin of the face, neck and trunk there were many acne papules and pustules and a great many comedones. Over the back and on the dorsal surface of the right thigh and buttock, there were several furuncles. There were small scars of previous lesions. The lymph



protein and carbohydrate content of the diet. On December 8, the blood sugar value was found to be above normal, and on the following day glycosuria was noted. The diet at this time was P 45, F 148, C 72 gm, 1,850 calories. It is apparent, therefore, that the maximum diet which this patient could tolerate on recovery on this admission is definitely less than that which was reached on the former admission. This probably illustrates the downward progression of the course of the disease, which so many observers have noted.

Between November 26 and December 14, the patient received 30 gm of calcium hexose phosphate daily. As compared with control cases in which none was given, the rate of increase in carbohydrate tolerance does not seem to have been accelerated by phosphate administration.

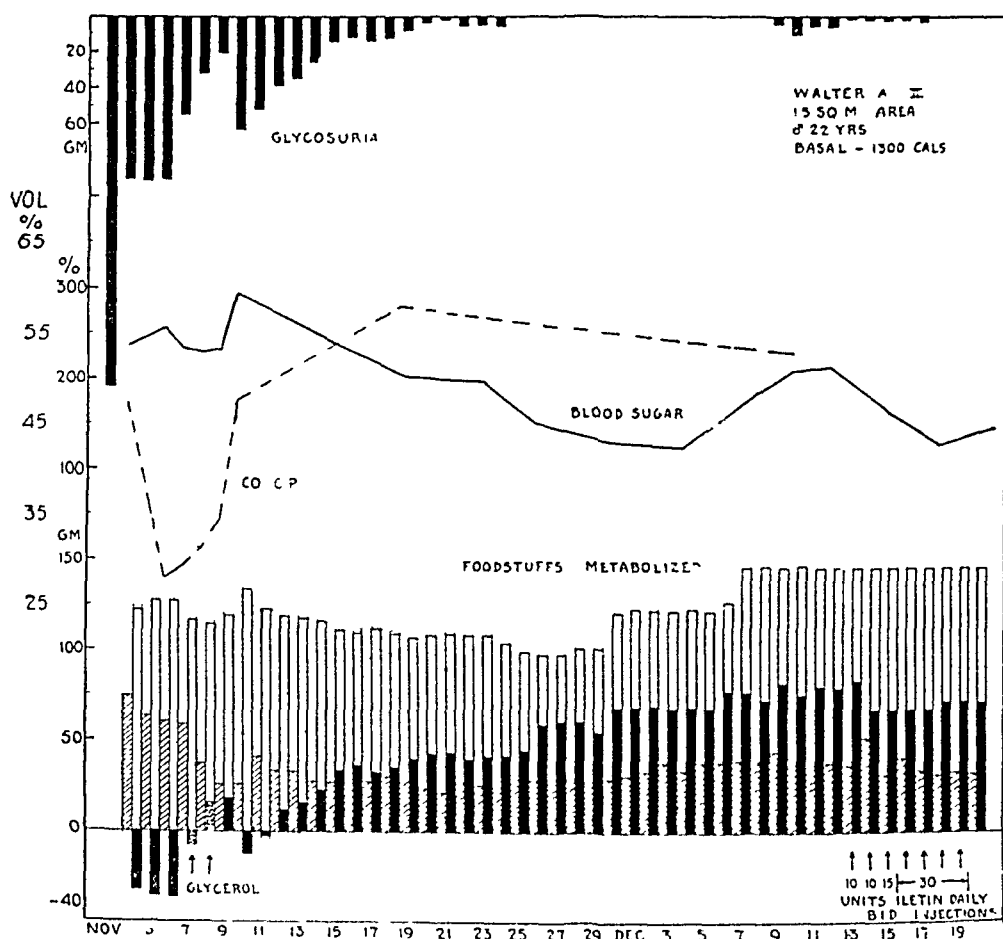


Chart 3 (Case 1)—Metabolism chart of Walter A, second admission. Black columns represent carbohydrate utilized or excreted, shaded columns, protein metabolized, unshaded, fat oxidized. All foodstuffs are given in grams. The diet given is not shown in the graph.

Between December 14 and 21, gradually increasing amounts of "iletin" (insulin, Lilly) were given, until glycosuria was stopped and the blood sugar value was again within normal limits, the diet remaining unchanged (1,850 calories).

Numerous respiration experiments were carried out on this patient. From the basal observations of the respiratory exchange, the basal heat production was calculated and the twenty-four calorie requirement was estimated. These experiments have been reported in a previous communication.<sup>3</sup> The experiments showed a diminished ability to oxidize glucose, as shown by a fall in respiration quotient following the ingestion of glucose.

lungs and heart were normal Blood pressure was systolic, 115, diastolic, 75 There were no other findings of importance except that there was a small white scar on the dorsum of the glans penis

The urine contained considerable sugar, acetone and diacetic acid The blood contained 0.22 per cent sugar

Diagnosis Diabetes mellitus, syphilis, acne vulgaris, furunculosis and retinitis proliferans

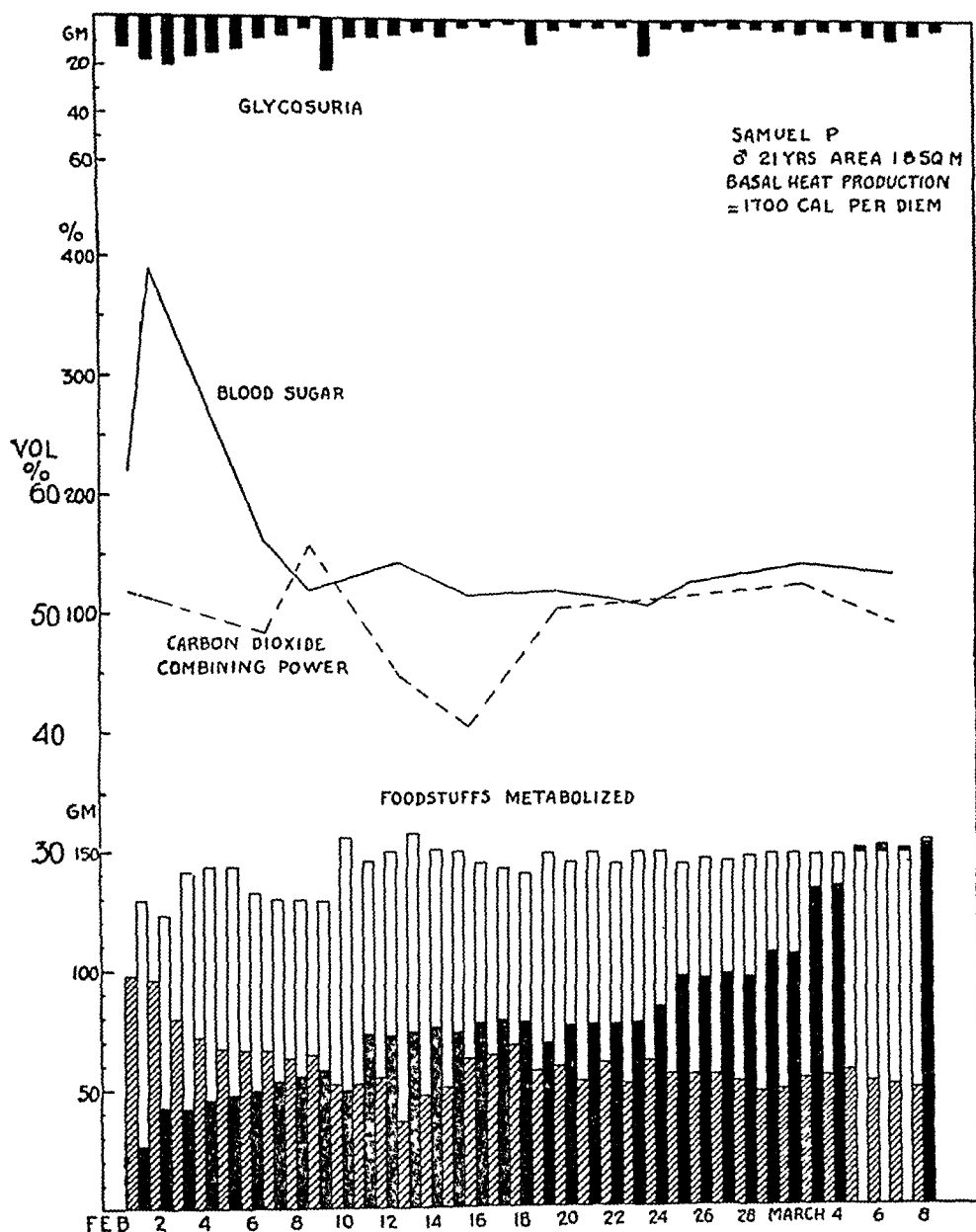


Chart 5 (Case 2) —Metabolism chart Foodstuffs metabolized are given in grams The black areas indicate carbohydrate, the shaded, protein, the unshaded, fat

*February 1* Blood Count Red blood cells, 5,464,000, white blood cells, 8,200, hemoglobin, 99 per cent Smear and differential count were normal

*February 2* The blood Wassermann reaction was negative

*Comment*—The course of the patient under treatment is best shown in Table 6, which contains all the data relative to diet and metabolism It is also shown graphically in Chart 5

nodes at the angle of the jaw, axillae and inguinal regions were palpable, but not much enlarged or tender. The extra-ocular movements were normal. The left pupil reacted to light directly but not consensually, the right pupil did not react to light directly, but did react consensually. Vision in the right eye was confined to light perception only.

*Ophthalmoscopic Examination* The left eye was normal. There was posterior polar cataract in the right eye; this disk outline was blurred, appar-

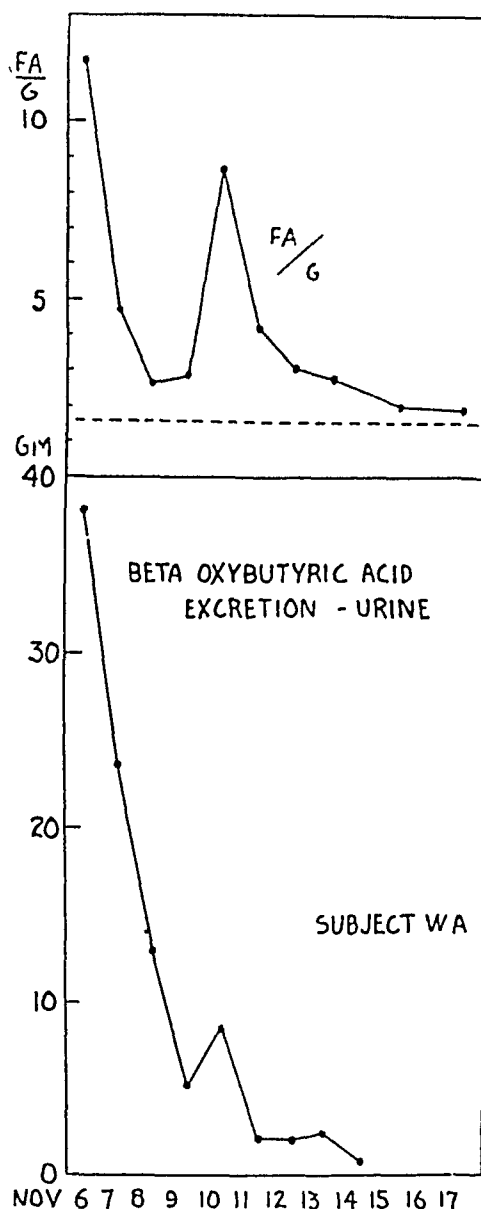


Chart 4 (Case 1) —Ketogenesis Note Tables 3 and 4

ently due to lenticular opacity. Extending outward from the disk, there was a streak of connective tissue running upward and to the nasal side until it met an area of choroidal atrophy from which strands of connective tissue extended out into the vitreous. Just below the margin of the disk there was another connective tissue strand also extending out into the vitreous and temporalward to the limit of ophthalmoscopic vision. **Diagnosis** Retinitis proliferans. The

From February 1 to 5, inclusive, the patient was given a diet furnishing only enough calories to cover the basal heat production, of which 10 per cent of the calories were obtained from protein. Fat and carbohydrate were in the proportions of Woodyatt,  $F = 2C$  plus  $P/2$ . On such a diet, very little change in the amount of sugar excreted was observed. The blood sugar fell from 0.39 per cent to 0.16 per cent.

From February 6 to 9, inclusive, the protein and carbohydrate of the diet were unchanged, but the fat was reduced to the lowest possible figure. At the end of this period, the blood sugar was within normal limits and the sugar excretion much reduced. This was probably only a continuation of the

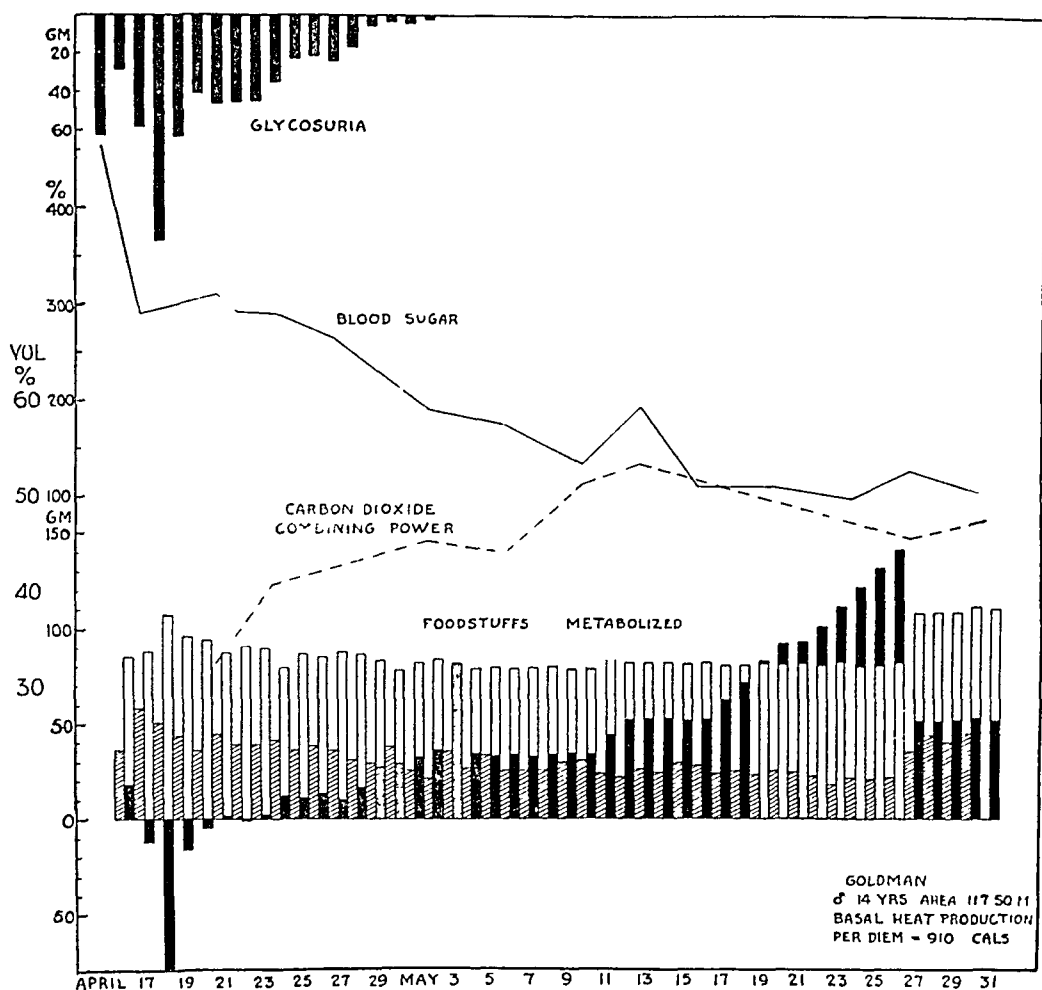


Chart 6 (Case 3)—Metabolism chart. Black columns throughout represent carbohydrate utilized or excreted in the urine. Stippled columns represent glycerol and carbohydrate. Protein metabolism (urine nitrogen grams  $\times 6.25$ ) is shown by the hatched columns. Estimated fat oxidized is shown by the unshaded columns.

improvement initiated in the preceding days. During this last period the excretion of organic acids was much reduced. Diacetic acid ceased to be detected first in the urine of February 7. On this day, the ratio of the available ketogenic substances, FA, to the total available antiketogenic substances, G, was found to be 1.5. The last observed diacetic acid excretion, February 6, occurred when the FA/G was 1.5. A small amount of acetone continued to be excreted throughout the patient's stay in the hospital, but as long as diacetic acid was

TABLE 6—*Diet and Metabolism in Cave 2*

Date, 1922	Urine Analysis						Blood		Diet Received				Foodstuffs Metabolized						Basal Heat Pro- duced	Calo- ries Re- ceived	Body Wt., kg	Body Sur- face, Sq M
	Volume, Cc	Sugar, Gm	Acce- tone	Dia- cetic Acid	Total Organic Acid, Cc N/10	Nitro- gen, Gm	Butyric Gm	Am- monia Nitro- gen Gm	Car- bon Dioxid., O P Vol %	Sugar, Gm	Pro- tein, Gm	Fat, Gm	Carbo- hydrate, Gm	Average Gm	Pro- tein, Gm	Fat, Gm	Carbo- hydrate, Gm	Avail- ible Gm				
2/1*																						
2/2	1,700	132	+	+	1,109	155			51.9	0.220	13.0	2.2	38.6	16.1	96.9	111	25.1	96	171	18	1,700	
2/3	2,300	198	+	+	1,176	153			51.2	0.392	41.2	147	62.1	103	95.6	138	42.6	112	167	15	1,508	
2/4	2,300	217	+	+	1,852	127					41.3	117.5	63.5	104	79.1	156	41.8	104	177	17	1,814	
2/5	2,450	174	+	+	1,781	115					41.7	148	62.2	103	71.8	158	47.0	102	175	17	1,812	
2/6	2,530	163	+	+	1,631	107					41.3	148	63.3	104	69.9	158	47.0	102	174	17	1,811	
2/7	2,200	147	+	+	940	106			48.1	0.161	41.1	3.6	63.1	89	66.2	117	48.7	102	163	16	1,653	
2/8	2,240	96	+	+	883	106					41.6	18	62.6	89	66.2	115	53.0	106	161	15	1,801	
2/9	2,160	69	+	+	843	101					43.9	2.1	62.2	88	63.1	115	53.3	106	160	15	1,451	
2/10	1,730	43	Trace	0	570	103			53.8	0.121	41.3	1.9	62.0	88	61.1	111	57.7	109	160	15	1,451	
2/11	2,640	225	+	+	2,640	81					15.1	150	71.9	113	52.1	49.1	49.1				1,873	
2/12	2,360	83	Trace	0		84					15.5	150	80.9	123	52.1	72.6	72.6				1,801	
2/13	2,000	80	Trace	0		88					16.6	150	80.3	122	55.0	72.3	72.3				1,918	
2/14	1,700	74	+	+		58			41.8	0.143	45.4	150	80.9	122	56.2	73.5	73.5				1,916	
2/15	2,300	52	+	+		76					15.7	150	80.7	122	47.5	73.5	73.5				1,917	
2/16	3,620	73	Trace	0		82	187		40.6	0.117	44.8	150	81.0	122	51.2	73.7	73.7				1,908	
2/17	3,600	35	Trace	0		101	123				46.1	151	80.6	123	63.1	77.1	77.1				1,922	
2/18	2,440	28	Trace	0		103	111				15.8	151	81.3	123	61.1	78.5	78.5				1,923	
2/19	2,810	19	Trace	0		110	149				16.9	151	80.1	122	68.8	78.2	78.2				1,921	
2/20	2,880	10.4	+	+		93	198				15.8	149	80.9	122	58.1	70.5	70.5				1,922	
2/21	2,560	40	Trace	0		96	186		50.6	0.120	45.2	151	81.3	123	60.0	77.3	77.3				1,923	
2/22	2,480	25	Trace	0		85	153	115			47.0	151	80.1	123	53.1	77.6	77.6				1,923	
2/23	3,610	30	V F T	0		98	131	112		0.115	46.1	150	80.6	122	61.2	77.5	77.5				1,917	
2/24	2,300	25	Trace	0		81	102				45.1	152	80.2	122	52.5	77.7	77.7				1,929	
2/25	2,900	14.5	Trace	0		99	299			0.107	45.4	151	99.7	141	61.8	85.2	85.2				2,000	
2/26	2,770	25	Trace	0		90	182	125			45.8	150	100.1	141	56.2	97.9	97.9				1,995	
2/27	3,600	40	Trace	0		90	105	122		0.129	46.5	150	101.0	143	56.2	97.0	97.0				2,000	
2/28	2,150	20	Trace	0		90	0.11	112			46.1	151	101.1	143	56.2	99.1	99.1				2,007	
2/29	2,300	30	Trace	0		85	106	102			15.9	151	100.6	143	53.1	97.6	97.6				2,000	
3/1	3,300	34	Trace	0		79	120	120			47.2	150	121.5	164	49.1	118.1	118.1				2,082	
3/2	2,420	43	Trace	0		80	101	101		0.123	46.2	150	121.5	163	50.0	117.2	117.2				2,081	
3/3	3,100	50	0	0		87	159	159			46.7	150	140.2	182	51.3	135.2	135.2				2,158	
3/4	2,500	37	0	0		88	112	112			47.9	151	140.1	183	55.0	136.1	136.1				2,171	
3/5	2,300	85	0	0		92	107	107			46.0	152	160.5	212	57.5	152.0	152.0				2,258	
2/6	3,200	64	0	0		86	117	117			46.8	151	159.7	202	53.7	153.3	153.3				2,248	
3/7	3,150	84	0	0		83	0.11	109		1.233	44.9	150	160.2	201	51.8	151.8	151.8				2,227	
3/8	2,710	67	Trace	0		65	0.9	0.9			47.6	150	160.1	203	40.6	154.1	154.1				2,249	
3/9	2,400	15	Trace	0				0.70			40.7	150	160.2			155.7					2,241	

\* Basal requirement = 1,670 + 170 = 1,840 calories per dlem  
 † Period I ‡ Period II § Period III

Calcium hexo sopherosphate 160 gm daily  
 Calcium glycerophosphate 50 gm daily

not present, the patient was allowed to sit up, so that the fat metabolism could no longer be calculated from the basal heat production

During Periods I, II and III, as shown in Table 5, this patient was given first inorganic phosphate,  $\text{Ca}_3(\text{PO}_4)_2$ , calcium hexose phosphate, and calcium glycerophosphate. During these periods, the actual utilization of carbohydrate increased, although a slight glycosuria persisted. The sugar content of the blood taken before breakfast remained within normal limits. In the light of similar marked improvement observed in cases treated without addition of large amounts of calcium and phosphorus to the diet, the improvement in this case is not attributed to the effect of calcium or phosphorus.

The balance between ingestion and excretion of calcium phosphorus and nitrogen are given in Table 7. In the case of calcium and phosphorus, no comment is offered. Nitrogen balance was negative throughout. This may be due to the large bulk of stools caused by the use of bran agar biscuits.

Respiration experiments on this subject have been reported in a previous communication.<sup>23</sup> The determinations of the basal metabolism and respiratory quotients are given in Table 8.

TABLE 8—*Basal Metabolism and Respiratory Quotients in Case 2*

	Basal Metabolism Calories per Hour	Respiratory Quotients	Percentage of Average Normal
Feb 15, 1922	69.3	0.75	97
Feb 19, 1922	70.0	0.83	98
Feb 22, 1922	64.1	0.77	90
Feb 24, 1922	68.8	0.80	96
Feb 27, 1922	70.1	0.77	98
Mar 6, 1922	67.7	0.83	95

CASE 3—*History*—Charles G., a schoolboy, aged 14 years, was admitted to the hospital on April 15, 1922, complaining of loss of weight. The paternal grandmother probably had diabetes. The patient's general health had been excellent. He had had scarlet fever at the age of 8 and measles at the age of 10. In July, 1921, he had had typhoid fever, with which he had been ill for two months. The attack was a mild one without complications. His present illness dated from the convalescence from typhoid fever. He had always eaten heartily. He had frequent attacks of "indigestion" with abdominal pain, vomiting and constipation. These attacks were relieved by rest, restricted diet and castor oil. He was habitually constipated, requiring purgatives most of the time. Before the attack of typhoid fever, the patient weighed 95 pounds (43.09 kg). Following this he weighed only 80 pounds (36.28 kg).

During the typhoid convalescence, an attempt was made to fatten the patient. In October, 1921, he began to drink a large amount of water, about 5 quarts a day. The urinary output increased in proportion. His appetite was unusually good. His weight decreased slowly. Sugar was discovered in the urine, but in spite of this he was given meat and candy and all that he could eat in an effort to make him gain weight. During the month prior to admission he lost 4 pounds (1.81 kg), the weight on admission to the hospital being 68 pounds (30.84 kg).

*Physical Examination*—The patient's height was 154.5 cm, he weighed 30.1 kg. The patient was a thin, poorly nourished, rather pale boy of 14 years. The skin was loose from loss of the panniculus. The mucous membranes were somewhat pale. Other than this no abnormalities were found.

The urine showed the presence of large amounts of sugar and acetone bodies. Blood examination revealed red blood cells 5,864,000, white blood cells, 5,920,

TABLE 7—*Nitrogen, Phosphorus and Calcium Balances in Case 2*

Period	Dates Inclusive	Food N, Gm	Urine N, Gm	Feces N, Gm	Total N Ex- creted, Gm	N Bal- ance, Gm	Food P, Gm	Added P, Gm	Total P In- take, Gm	Urine P, Gm	Feces P, Gm	Total P Ex- creted, Gm	P Bal- ance, Gm	Food Ca, Gm	Added Ca, Gm	Total Ca In- take, Gm	Urine Ca, Gm	Feces Ca, Gm	Total Ca Ex- creted, Gm	Ca Bal- ance, Gm
I*	Feb 15-19	36.6	48.9	6.3	57.2	-18.6	5.02	16.70	21.72	5.26	15.32	20.58	+1.14	2.79	38.80	41.59	1.54	25.68	27.22	+14.37
II†	Feb 20-26	51.4	64.2	12.0	76.2	-24.8	10.09	32.40	42.49	9.17	32.81	41.98	+0.51	4.02	52.61	56.13	1.90	46.40	48.30	+9.33
III‡	Feb 27-Mar 6	59.7	68.7	10.3	88.0	-28.3	11.93	52.76	64.69	12.61	57.83	70.44	-1.75	5.03	68.56	73.59	2.17	71.95	74.12	+0.13

\*  $\text{Ca}_3(\text{PO}_4)_2$ , 100 gm

† Calcium glycerophosphate, 400 gm

‡ Calcium hexose phosphate, 420 gm

hemoglobin, 100 per cent, with a normal differential count. The Wassermann reaction was negative. The blood sugar content was 0.465 per cent.

*Comment*—The patient was at first given a diet of 1,300 calories, estimated to cover the normal requirement for his size and age. Subsequently this was found to be greatly in excess of the actual requirement (Table 9). At the end of one week on this diet the sugar excretion had considerably diminished, the blood sugar remaining high. For two days, April 23 and 24, the total calories of the diet were reduced to 450 by diminishing the fat from 108 to 15 gm. The blood sugar remained stationary, the carbon dioxide capacity of the plasma increased, and there was a coincident decrease in excretion of acetone bodies.

The basal heat production was found to be 910 calories a day. On April 25, a diet was given furnishing 1,000 calories for an estimated requirement of basal metabolism plus 10 per cent. The patient was kept in bed and showed little tendency to activity, as he was ill and weak.

Between April 25 and 29, a further decrease in urine sugar excretion occurred and a further diminution in acetone elimination. On the twenty-ninth, the diet formula was unchanged except that 31 gm of glycerine were substituted for

TABLE 10—*Ketogenesis in Case 3*

Date	Foodstuffs Metabolized			Total Acetone Bodies Excreted, Gm	Excess Ketogens Milli-mols E	Ketogens Total Milli-mols K	Ketogens Oxidized Milli-mols $K-E=K'$	Anti-ketogens Milli-mols A	Ratio K A	Ratio K' A
	Protein, Gm	Fat, Gm	Carbohydrate, Gm							
4/19/22	43.6	96	-16.5	28.1	270	435	165	92	4.7	1.8
4/20/22	35.5	94	-5.4	28.5	274	407	133	137	3.0	1.0
4/21/22	44.1	88	1.2	18.8	180	408	228	258	1.6	0.9
4/22/22	38.9	91	0.3	32.2	310	406	96	175	2.3	1.8
4/23/22	38.9	90	1.9	15.3	147	402	255	186	2.2	1.4
4/24/22	41.7	80	11.5	12.5	120	376	256	244	1.5	1.1
4/25/22	36.1	87	10.5	14.6	140	385	245	224	1.7	1.1
4/26/22	38.1	85	13.0	13.1	126	384	258	243	1.6	1.1
4/27/22	35.9	88	9.6	11.0	106	389	283	218	1.8	1.3
4/28/22	30.9	87	16.0	6.9	66	373	306	181	2.1	1.7
4/29/22	28.9	83	27.3	3.4	33	354	321	285	1.5	1.4
4/30/22	37.5	78	28.8	2.0	19	358	339	324	1.1	1.04
5/ 1/22	25.2	82	32.2	1.4	13	341	328	306	1.1	1.07
5/ 2/22	21.7	84	36.3	1.2	12	341	329	320	1.1	1.03
5/ 3/22	35.5	82	81.5	0	0	367	367	613	0.6	0.6

31 gm of carbohydrate. The result was an immediate sharp decrease in both sugar and acetone excretion. Following this, the diet consisted of 1,000 gm of 5 per cent vegetables, furnishing only 236 calories. By May 3, glycosuria was no longer present, and only minimal amounts of acetone bodies were excreted.

From the data available in this case, it is possible to calculate the ratio of ketogenic to antiketogenic substances in the patient's metabolism at the time of cessation of ketonuria. Between April 27 and 30, the beta hydroxybutyric acid excretion decreased from 7.3 gm to 1.3 gm, and the ratios FA/G diminished from 2.43 to 1.50. The ratios at the time of cessation of acetone body excretion lie between the values of 1.49 and 1.55, corresponding closely with the theoretical metabolism of one molecule of diacetic acid with one molecule of hexose (Table 10 and Chart 7).

The further course of the patient was one of rapid improvement. By May 10, the blood sugar was at the normal level, and the alkaline reserve of the plasma was normal. A slight increase in carbohydrate intake resulted in a return of the blood sugar to a higher level on the thirteenth. At this time, administration of calcium hexose phosphate was started. Without decreasing the diet, the



TABLE 9—Diet and Metabolism in Case 3

Date	Urine Analyses						Blood		Diet Received			Foodstuffs Metabolized					Calcu- lated Re- quire- ment	Body Wt., Kg	Sur- face Area, Sq M
	Volume, Cc	Sugar, Gm	Acce- tone	Diacetic Acid	Total Oxy- butyric Acid, Gm	Am- monia, Gm	Total Nitro- gen, Gm	Car- bon Dioxid., C P, Vol %	Sugar, %	Pro- tein, Gm	Fat, Gm	Carbo- hydrate, Gm	Avail- able F A, Gm	Avail- able Gm	F A — G	Food, Calo- ries			
4/15*	1,640	62.3	++	++	21.3	2.30	8.47		0.465	30.8	107	45.9					1,310	30.1	1.17
4/16	1,770	28.3	++	++	21.8	2.42	5.69		0.290	32.3	107	41.7					1,310	30.5	
4/17	2,300	57.5	++	++	25.3	3.20	9.24			31.0	107	44.7					1,306	30.0	
4/18	2,120	116.6	++	++	23.6	3.19	8.10			29.1	107	46.0				5.92	1,307	30.3	
4/19	2,500	62.5	++	++	18.7	2.65	6.08			32.1	109	45.4				4.10	1,327	29.7	
4/20	2,500	40.0	++	++	19.0	2.41	5.68			29.6	108	46.6				2.79	1,311	30.2	
4/21	3,244	45.4	++	++	12.5	2.46	7.06	32.4	0.310	29.6	103	44.7				3.17	1,305	30.4	
4/22	3,600	45.0	++	++	21.5	2.33	6.23		0.291	30.7	111	46.2				2.92	1,442	30.8	
4/23	3,250	44.3	++	++	10.2	1.97	6.22			31.2	15	46.0				2.08	1,000	31.0	
4/24	3,840	34.5	++	++	8.3	1.75	6.63	40.0	0.230	29.5	81	32.6				1.88	1,007	31.3	
4/25	3,250	22.1	++	++	9.7	1.54	5.79			31.4	82	33.3				1.75	1,026	31.9	
4/26	3,066	20.3	++	++	8.7	1.76	6.10		0.265	29.4	82	33.1				2.43	1,016	31.4	
4/27	3,760	23.5	++	++	7.3	1.25	5.75			30.6	81	32.5				2.17	1,012	32.5	
4/28	3,300	16.5	++	++	4.6	1.10	4.95			31.1	82	1.2				1.67	1,026	32.8	
4/29†	3,560	4.9	+	—	2.26	0.77	4.63			34.1	81	1.2				1.70	1,058	32.8	
5/1	2,860	3.4	+	—	1.33	0.65	6.01			13.5	2.6	28.8				1.55	236	33.1	1.21
5/2	3,200	4.0	—	—	0.92	0.57	4.03	45.3	0.190	13.5	2.6	28.2				1.49	236	33.1	
5/3†	3,540	1.8	—	—	0.79	0.29	3.47			13.6	2.6	28.1				0.82	1,236	33.5	
5/4†	3,700		—	—	0.05	0.62	5.68			31.2	82	38.1					1,022	33.0	
5/5	3,940		—	—	1.24	0.61	4.20			30.7	81	33.9					1,021	32.9	
5/5	3,820		—	—	1.63	0.65	5.35			31.4	82	32.8					1,023	32.6	
5/6	4,100		—	—	1.51	0.57	4.03	41.0	0.174	31.4	82	33.5					1,031	32.1	
5/7	4,200		—	—	0.39	0.57	3.99			29.0	83	32.5					1,019	31.9	
5/8	3,355		—	—			4.03			29.0	82	33.7					1,019	31.9	
5/9	4,400		+	—	3.99	0.65	3.88			29.0	84	34.4					1,012	31.9	

\* Basal heat production = 910 calories + 10 per cent (91 calories) = 1,001 calories

† 31 gm glycerin added to diet

‡ 80 gm glycerin added to diet

Reports in December, 1922, and January, 1923, indicate that he was having a great deal of trouble with digestive disturbances and great difficulty on account of constipation

During the patient's stay in the hospital, he was the subject of several respiration experiments which have been reported in a previous paper.<sup>3</sup> These experiments showed that at the time of marked glycosuria and hyperglycemia there was complete inability to oxidize glucose during a period of two hours after ingestion. There was much greater rapidity of oxidation of ingested calcium hexose phosphate. Coincident with the increase in sugar utilization, respiration experiments showed an improved ability to oxidize glucose ingested

The basal metabolism tests are summarized below

*April 21* The basal metabolism rate was 25 per cent below the average normal—379 calories an hour  $\times 24 = 910$  calories a day

*May 3* The basal metabolism rate was 32 per cent below the average normal—344 calories an hour  $\times 24 = 826$  calories a day

*May 8* The basal metabolism rate was 34 per cent below the average normal—334 calories an hour  $\times 24 = 802$  calories a day

*May 19* The basal metabolism rate was 36 per cent below the average normal—322 calories an hour  $\times 24 = 773$  calories a day

*May 26* The basal metabolism rate was 35 per cent below the average normal—325 calories per hour  $\times 24 = 780$  calories a day

*CASE 4—History*—Howard M., a schoolboy, aged 16 years, was admitted July 7, 1922, complaining of thirst and loss of weight. The family history and past history were unimportant. The patient had been in good health until late November, 1920, at which time he noted that he was more thirsty than usual and that he was drinking large amounts of water. Frequent urination was noted, with three or four voidings at night. In spite of a large food intake, a loss of 15 pounds (6.8 kg) in weight occurred in the course of a few weeks. His weight prior to the onset had remained stationary at about 85 to 90 pounds (38.5 to 40.8 kg) between the ages of 14 and 16. His first physician prescribed arsenic and water restriction. Two or three weeks later, the urine contained sugar. The diet prescribed was practically carbohydrate free, but allowed unmeasured amounts of fat and protein. Under this regimen, glycosuria continued until March, 1921. At this time, starvation was commenced. The urine ceased to contain sugar. The diet was gradually increased until the patient was comfortable. He gained slightly in weight. In August, 1921, glycosuria was again discovered. From this time on sugar occurred in the urine at intervals of two to three weeks. On each occurrence, the patient was starved until sugar free, and the diet again built up. In this process, only the carbohydrate content of the diet was considered. The amount of carbohydrate which he could take without glycosuria decreased. At the time he left his home to enter the hospital, he had no glycosuria. The diet was much under maintenance, containing only 8 gm of carbohydrate. In traveling, he again developed glycosuria.

*Physical Examination*—The patient's height was 153 cm, he weighed 32 kg. The examination was entirely negative, except for evidence of extreme emaciation, the presence of pyorrhea alveolaris, sluggish tendon reflexes and small characteristic xanthomas situated on the dorsa of the hands between the thumbs and index fingers. The blood pressure was systolic, 100, diastolic, 75. Temperature, pulse and respirations were normal. Blood examination revealed 4,264,000 red blood cells, 8,200 white blood cells and 70 per cent of hemoglobin. Blood smear and differential count were normal. The Wassermann reaction was negative. The blood sugar on July 8 was 0.195 per cent. Urine examination showed the presence of sugar but no acetone, albumin or casts.

*Treatment and Course*—The course of the patient under treatment can be followed best by reference to the diet and metabolism chart given in Table 11. The patient's dietary requirement was estimated to be about 1300 calories a

blood sugar again returned to normal levels, and it was possible to increase the diet by increase of carbohydrate from 52 to 142 gm and of total available glucose from 79 to 159 gm. The increase in diet was discontinued because it was not desirable to push the increase to the tolerance limit. By the use of more fat and less carbohydrate, the patient could take an adequate diet. He was discharged on May 31 with instructions to restrict the diet to from 1,500 to 1,700 calories.

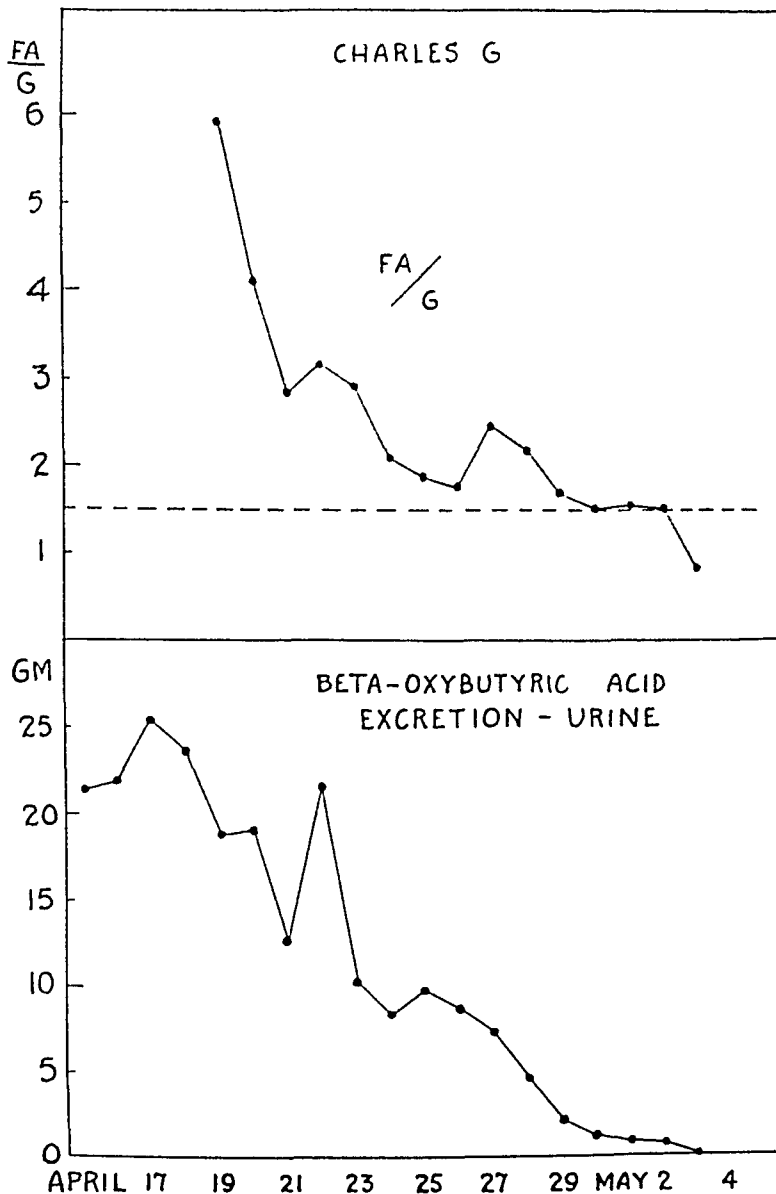


Chart 7 (Case 3)—Ketogenesis. The FA/G ratios were calculated from the amounts of foodstuffs metabolized by the patient, not from the diet given.

Reports from the patient during the summer showed that he was able to keep the urine free from sugar, and several blood examinations showed a normal fasting sugar content.

During the fall and early winter of 1922, occasional glycosuria was reported, easily controlled by the patient himself by means of green vegetable diet.

day, though subsequent determination of the basal metabolism (995 calories) showed the basal requirement to be 1,100 calories. Calculation of the fat metabolized is based on the latter figure during the period in which the patient was confined strictly to bed.

The initial diet furnished 1,300 calories daily from July 8 to 16, with 10 per cent of the total calories from protein. In all diet prescriptions the relation of the foodstuffs is expressed by the formula  $F = 2C$  plus  $P/2$ . On this diet, the patient's progress was apparently satisfactory, the urine contained no acetone or glucose, the blood sugar fell at first from 0.195 per cent to 0.175 per cent. There was a considerable loss of nitrogen daily, so that the amount of protein in the diet was doubled, keeping the same total caloric value of the diet.

The effect of the increase in protein in the diet between July 16 and 20 was most undesirable. On the second day following the increase a trace of sugar appeared in the urine. This was followed by marked glycosuria, which persisted during the whole remaining period of observation.

A green vegetable diet was given on July 23, and for the days following this restriction of the diet to the bare maintenance requirement, with simultaneous reduction of the protein intake to 12 gm, had no appreciable effect on the glycosuria.

For a period of seven days—from July 25 to 31—30 gm of glycerine were substituted for an equal weight of carbohydrate in the diet. This caused a prompt cessation of acetonuria, which had existed prior to the substitution. It had an interesting effect on the relationship of the calculated FA/G ratio to the disappearance of acetone from the urine, which it is well to discuss at this point.

The first qualitative test for acetone in the urine was obtained on July 18. Prior to this date, the calculated FA/G ratios were all less than 1.5. On the eighteenth, the ratio was slightly more than 1.5 coincident with acetonuria. The ratios increased considerably and then decreased to about 1.5 again, and acetonuria, as measured by qualitative tests, again decreased to a mere trace. A trace of acetone continued to be excreted even when the FA/G ratio fell to 1.37. On the next day, when the substitution of glycerine was commenced, there was a sharp increase in the calculated FA/G ratio (2.2—2.5), with a coincident disappearance of ketonuria. This phenomenon is difficult to explain. It seems probable that the ingested glycerine had produced an antiketogenic effect even though 40 to 45 per cent of its weight appeared in the urine as sugar.

After discontinuing the use of glycerine as a substitute for carbohydrate, a further great increase in the FA/G ratio was noted. It is of interest to observe that there was a lag in the appearance of acetone bodies in the urine, none being present on August 1, when the ratio was 3.07. Such a ratio would indicate that two molecular proportions of diacetic acid had been completely oxidized in the presence in the metabolism of one molecular proportion of glucose.

Beyond August 3, the calculation of the amount of fat metabolized had not been carried out for the reason that the patient was no longer confined strictly to bed, making the total heat production impossible to estimate.

The patient continued under observation during seven weeks more. The remainder of the metabolism chart will not be given in detail for the sake of brevity. It may be summarized briefly. The diet was kept at about 1,000 calories, very low in protein. Glycosuria and hyperglycemia persisted throughout, and small amounts of acetone bodies were excreted.

From August 15 to 24, 30 gm of calcium hexose phosphate were ingested daily without any change for better or worse in sugar utilization.

At various times between August 25 and September 22 the patient was given injections of "Iletin" furnished by the Eli Lilly Company. The preparations of this substance obtainable at that time were of little potency, so that no practical benefit was derived from the treatment.

TABLE 11—*Diet and Metabolism in Case 4*

Date	Urine				Blood		Diet Received			Foodstuffs Metabolized						Calo- ries Re- ceived	Body Wt., Kg	Calo- ries Re- quired
	Volume, Cc	Sugar, Gm	Acetone	Diacetic	Total Nitro- gen, Gm	Carbon Dioxid., C P Vol %	Sugar, %	Pro- tein, Gm	Fat, Gm	Carbo- hydrate, Gm	Gly- cerin Gm	Pro- tein, Gm	Fat, Gm	Carbo- hydrate, Gm	Avail- able F A, G	Avail- able G,	F A — G	
7/ 8/22*						38.8	0.195	31.9	105.4	45.6						1,208	32	1,100
7/ 9/22	2,650	0	0	0	?			32.2	105.6	45.0						1,299		
7/10/22	3,070	0	0	0	7.77			32.0	107.0	45.6		48.5	76.8	45.6	91.4	81.5	1.12	
7/11/22	3,570	0	0	0	7.63			33.3	106.5	44.2		47.7	77.8	44.2	91.9	79.7	1.15	
7/12/22	3,700	0	0	0	7.95		0.175	32.3	105.9	44.9		49.7	76.4	45.0	91.7	81.3	1.13	
7/13/22	1,840	0	0	0	?			33.0	106.6	45.0						1,311		
7/14/22	3,340	0	0	0	6.86			32.0	105.7	45.1		39.7	80.8	45.1	91.0	76.2	1.19	
7/15/22	3,460	0	0	0	5.52			33.0	106.5	45.7		34.5	82.9	45.7	90.5	71.0	1.22	
7/16/22	5,050	0	0	0	9.93			33.6	106.1	45.7		56.4	77.8	45.7	95.9	76.1	1.26	
7/17/22	4,740	Trace	0	0	9.73			67.3	106.2	45.3		61.1	75.8	45.3	96.4	78.3	1.23	
7/18/22	4,640	12.9	+	0	9.84			68.2	106.5	45.3		58.4	82.6	45.3	101.2	64.8	1.59	
7/19/22	4,760	36.4	+	0	11.12			68.0	105.9	45.0		67.0	83.4	45.0	111.5	18.0	2.32	
7/20/22	5,000	30.0	+	0	10.71			50.0	109.3	42.3		12.3	83.4	45.0	105.9	59.5	1.78	
7/21/22	4,460	14.3	+	0	7.99		0.267	50.6	109.5	41.8		19.9	84.2	45.0	99.7	64.0	1.54	
7/22/22	5,210	13.7	Trace	0	8.21			51.1	110.5	41.3		51.3	85.4	45.0	97.9	63.8	1.50	
7/23/22†	3,160	11.0	Trace	0	7.38			13.0	4.0	40.0		15.6	85.4	45.0	97.9	64.0	1.53	
7/24/22	4,370	18.9	Trace	0	6.97		0.232	16.7	118.5	54.5		43.6	83.4	45.0	95.2	69.2	1.37	
7/25/22	4,280	24.2	0	0	7.65			12.3	87.0	10.7	30	35.3	95.4	45.0	102.1	10.5	2.20	
7/26/22	4,320	24.1	Trace	0	5.22			12.5	87.6	10.7		35.3	96.8	45.0	102.1	41.8	2.28	
7/27/22	4,610	27.3	0	0	4.81			12.3	87.0	10.7	30	30.1	99.1	45.0	103.1	10.7	2.53	
7/28/22	4,900	28.0	0	0	5.25		0.268	11.8	88.7	10.0	30	32.8	98.5	45.0	103.7	40.9	2.53	
7/29/22	4,920	16.2	0	0	?			12.5	87.7	10.3	30					1,013		
7/30/22	7,340	16.1	0	0	5.69			12.5	87.7	10.3	30	31.9	87.8	21.2	95.8	53.3	1.80	
7/31/22	7,350	13.8	0	0	5.02			12.5	88.6	9.7	30	31.4	93.0	25.9	98.2	53.4	1.84	
8/ 1/22	6,640	33.3	0	0	6.80			25.8	81.6	34.1		42.5	99.2	0.8	108.8	35.4	3.07	
8/ 2/22	5,700	39.4	Trace	0	6.12			25.4	80.6	34.0		38.2	103.7	—5.4	110.9	27.2	1.06	
8/ 3/22	6,140	61.4	++	0	6.77		0.333	30.2	81.6	31.9		42.3	111.3	—26.5	119.6	11.1	10.8	• 1,052

\* Basal, 895 calories + 10 per cent (100 calories) = 1,095 calories required

† 1,000 gm green vegetables

duction of 995 calories a day. The basal requirement for the period of confinement to bed was estimated at 10 per cent above this figure, in round numbers 1,100 calories.

**CASE 5—History**—Auer, a schoolboy, aged 17 years, was admitted to the hospital on Oct 19, 1922, complaining of thirst, excessive urination and of feeling tired. His family history was essentially negative. His past history was negative, except that he had had whooping cough in infancy and two attacks of pneumonia, at the ages of 7 months and 7 years. His health had been excellent in every way. He had led the active outdoor life of a schoolboy, participating in athletics until the onset of the present illness, which began three weeks prior to admission. The onset was sudden, with excessive thirst and polyuria. A week later the patient noted a feeling of weakness and tired easily. His weight, which had been 126 pounds (57.15 kg) decreased to 114 pounds (51.71 kg) in three weeks. Sugar was found in the urine by his physician, who sent him at once to the hospital.

**Physical Examination**—The patient's height was 171 cm, and he weighed 50 kg. He was a ruddy faced boy, tall, erect, but rather thin. The examination revealed no abnormalities except extreme dryness of the skin and diminished tendon reflexes, the knee jerks being absent. The blood contained 5,800,000 red blood cells and 9,160 white blood cells. There was 95 per cent of hemoglobin. The Wassermann reaction was negative. The blood sugar was 0.223 per cent, the carbon dioxide combining power 40 volumes per cent. Urine. Specific gravity, 1.055, sugar, heavy reduction, a heavy trace of albumin, acetone and diacetic acid were present. The course of illness under treatment can be outlined best by reference to Table 12, in which are given the data regarding diet and metabolism. A graphic metabolism chart is shown in Chart 8. Reference to Table 12 shows that the FA/G ratio at the threshold of ketonuria indicated approximately the metabolism of two molecules of ketogens per molecule of antiketogen.

For the sake of brevity the portion of the chart beyond November 2 has been omitted, as the progress of the case is shown graphically in Chart 8.

The diet given on discharge from the hospital furnished nearly 2,000 calories. The patient could live on this by restricting activity, but it was far below that required by a normal boy of his age.

#### ANTI-KETOGENESIS

The calculations of the ratios of ketogenic to antiketogenic substances in our series have all been based on the estimates of the amounts of the various foodstuffs oxidized each day. So far as protein metabolism is concerned, the results are quite accurate. It is highly probable that the difference between the amount of carbohydrate ingested and the amount excreted is oxidized, especially when the amount is small. The most questionable calculation is that regarding the amount of fat oxidized, which depends for its reliability on the accuracy with which the total heat production for the day is estimated. In the cases in which the ketogenic balance have been determined, considerable effort was made to keep the energy expenditure as near to the measured basal heat production as possible. The first four cases of this report were kept extremely quiet, and it is highly probable that the estimates of daily heat production (basal metabolism plus 10 per cent) are within 100 calories of the actual metabolism. This would give an accuracy to the fat estimates of  $\pm 10$  gm a day.

After leaving the hospital, the patient was again subjected to starvation by his mother. She was able to cause the disappearance of glycosuria by this method, but was unable to build the diet up to more than 700 calories a day.

It is of interest to note that in the respiration experiments which were performed on this patient, the respiratory exchange following the ingestion of glucose showed an approximately normal rate of increase in respiratory

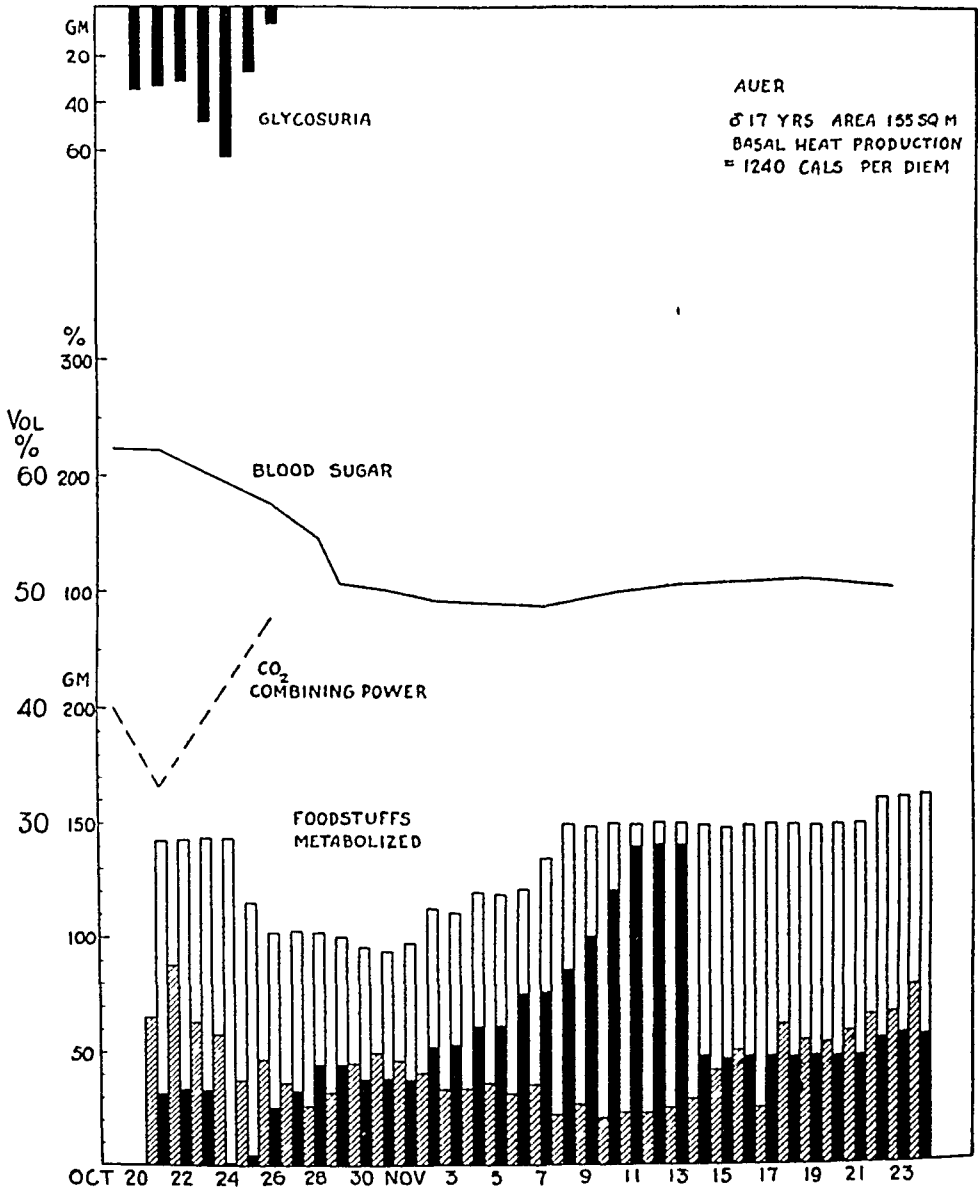


Chart 8 (Case 5) —Metabolism chart. Black columns throughout represent carbohydrate in grams utilized or excreted in the urine. Protein metabolism in grams a day is shown by the cross hatched columns (urine nitrogen grams  $\times$  625). The fat oxidized daily is shown by the total height of the unshaded columns, in this case only the roughest estimate of fat was possible because of the activity of the patient.

quotients. These experiments were performed on Sept 5, 1922. They have been reported in the first paper of this series.<sup>23</sup> The basal metabolism on this occasion was 16 per cent below the average normal, giving a basal heat pro-

A comparison of the results of computing the ketogenic balance by means of Woodyatt's factors<sup>12</sup> or by those of Shaffer<sup>11</sup> shows that the estimate of ketogenic substances is generally about 15 per cent higher when Shaffer's factors are used. The difference in the two methods is not sufficient to alter the general interpretation of the results (see the last three columns of Table 10). Woodyatt's ratio  $\frac{FA}{G}$  is the ratio of the weights of ketogenic to antiketogenic materials. It is readily converted into a molecular ratio by dividing 1.5, so that it becomes  $\frac{FA}{1.5G}$ , and is approximately the same as  $K/A = 1/1$ .

A graphic illustration of the close parallelism between the  $FA/G$  ratios and the excretion of B-oxybutyric acid on corresponding days, in two patients, is given in Figures 4 and 7. In Figure 7, the ketonuria ceased sharply at the point at which the  $FA/G$  ratio  $= 1.5$ , corresponding to a molecular ratio of 1:1. In Figure 4, the ratio at which ketonuria ceased is somewhat above this figure,  $FA/G = 2.0$  or a molecular ratio of 1.3:1.

At the point of disappearance of ketonuria, the  $FA/G$  ratio is almost always close to 1.5:1. During the first admission of Walter A., Table 1, acetoneuria ceased on January 4, when the  $FA/G$  ratio was 1.8, indicating a molecular ratio of 1.2:1. During the second admission of this patient (Table 3), ketonuria ceased when the  $FA/G$  ratio was 1.9. In the case of Samuel P., ketonuria became negligible when the  $FA/G$  ratio was 1.5 (Table 6). Also in the case of Charles G. (Table 9), the same ratio was obtained on the last days of ketonuria.

In the case of Howard M. (Table 11), tests for acetone in the urine were negative prior to July 18. At the threshold of ketonuria in this case, the  $FA/G$  ratio changed from 1.2 on the seventeenth to 1.6 on the eighteenth. At the point of disappearance of the ketonuria, a much higher ratio was found,  $FA/G = 2.5$ . On the recurrence of ketonuria, the  $FA/G$  ratio was slightly over 3.0, indicating the existence of a molecular ratio of  $K/A = 2:1$ .

The foregoing calculations of the ketogenic balance show that usually, but not always, the molecular ratio is 1:1 at the threshold. When excessive ketogenesis exists, Shaffer<sup>11</sup> found that predictions of the ketone excretion based on the equimolecular ratio were too high. In Table 4 and Table 10 a calculation has been made of the ratio of molecules of completely oxidized ketogens to completely oxidized anti-ketogens. In order to determine this relationship, the total ketone bodies excreted were taken as equal to the amount excreted in the urine plus 50 per cent to allow for excretion through the lungs<sup>11</sup>. Since the determination of keto acid was expressed in terms of beta-oxybutyric acid, the weight of beta-oxybutyric acid divided by 0.104 gives the number of millimols of ketogenic material excreted. If the total number of ketogenic millimols ( $K$ ) is known, and from this number one subtracts the number of millimols excreted ( $E$ ), the difference



TABLE 12—*Diet and Metabolism in Case 5*

Date	Urine				Blood		Diet Received			Foodstuffs Metabolized					Calo- ries Re- ceived	Calo- ries Re- quired	Body Wt., Kg	Surface Area, Sq M
	Volume, Cc	Sugar, Gm	Ace- tone	Dia- cetic	Total Nitro- gen, Gm	Carbon Dioxid, C P Vol %	Sugar, %	Pro- tein, Gm	Fat, Gm	Carbo- hy- drate, Gm	Avallable		FA G					
											FA, Gm	G, Gm						
Oct 19-20	1,670	36.9	+	+	15.9	40.2	0.223	18.7	112.9	63.8	65.5	104	31.1	123	93	1.6	1,666	1,360
Oct 20-21	1,900	34.7	+	+	10.8	33.1	0.222	18.3	142.7	63.6	88.0	93	33.1	123	80	1.3	1,638	
Oct 21-22	1,300	32.5	+	+	14.2			20.4	143.1	65.2	63.0	104	32.7	123	80	1.5	1,660	
Oct 22-23	2,300	50.0	+	+	10.0			19.5	143.1	63.8	57.5	120	0.7	134	46	2.9	1,636	
Oct 23-24	2,940	64.9	+	0	9.2			19.3	99.5	32.3	37.5	128	4.1	133	39	3.4	1,144	
Oct 24-25	2,350	28.2	+	0	0.1	47.8		18.9	99.2	33.8	46.5	115	25.0	125	64	2.0	1,150	
Oct 25-26*	2,300	8.8	0	0	7.5			19.1	99.9	32.7	26.7	93	32.7	125	64		1,118	
Oct 26-27	3,000	0	0	0	5.7		0.175	15.0	3.1	44.6	25.9	102	44.6				372	
Oct 27-28	2,480	0	0	0	4.2		0.127	15.0	3.1	44.6	25.9	102	44.6				370	
Oct 28-29	1,820	0	0	0	5.2		0.107	15.0	3.1	44.0	32.4	100	44.0				370	
Oct 29-30	3,140	0	0	0	5.2			26.0	94.2	37.9	44.9		37.9				1,124	
Oct 30-31	2,430	0	0	0	7.2			25.5	94.4	37.8	49.4		37.8				1,143	
Oct 31	2,630	0	0	0	7.9		0.102	27.0	97.2	37.8	46.4		37.8				1,169	
Nov 1-2	1,950	0			7.4			27.9	112.5	51.7	40.3		51.7				1,372	
Nov 2-3	2,300				6.5		0.084	28.8	110.8	52.5	33.2		52.5				1,322	
Nov 3-4	2,250				5.3												1,322	

\* Basal metabolism = 1,240 calories + 10 per cent (124 cals) = requirement, 1,364 calories

about 40 per cent of the weight of glycerol ingested. It is apparent that so far as the remaining 60 per cent of glycerol were oxidized, it would be available for antiketogenesis without increasing glycosuria or hyperglycemia. The energy value of a gram of glycerol is 4.3 calories, according to Emery and Benedict.<sup>27</sup>

In a previous communication experiments were reported on the effects of glycerol on the respiratory exchange.<sup>26</sup> It was found that almost identical curves of changes in the respiration quotient were produced by glycerol and glucose when compared in the same diabetic subject. With normal subjects, ingestion of glycerol produced a fall in respiratory quotients. It seems highly probable that glycerol may be oxidized in the body in large amounts. This oxidation may proceed in stages as from glycerol to glyceric aldehyde, so that the oxygen consumption in the early stages would outweigh the carbon dioxide production, resulting in lower quotients than those to be expected from the complete immediate oxidation of glycerol.

One word of warning in regard to the use of glycerol must be given. Some persons appear to be sensitive to glycerol, or to an impurity in it. Vomiting and diarrhea occasionally occurred, and in some subjects urticarial eruptions have been noted. These undesirable effects are noted on the occasion of the first dose, if they are noted at all. When they occur it is not advisable to repeat the dose.

An important point in the therapy of diabetes is the control of the level of protein metabolism. Carefully studied patients with complete diabetes ( $D/N = 3.65$ ) have almost always shown the disease in its maximum severity following a high protein-fat regimen. In the present series, Case 4, Howard M., illustrates very well the unfavorable effect on the carbohydrate tolerance produced by raising the level of protein metabolism. It is difficult to explain just how this unfavorable effect is brought about. In our larger series of cases, similar observations have been made again and again.

During diabetic acidosis the level of protein metabolism is invariably high. It is rarely to be found to furnish more than 30 per cent of the total number of calories, even in severe acidosis. In the case of Walter A. (Table 1), Dec. 18, 1921, the calories derived from protein would have been about 45 per cent of the total heat production were none of the heat of protein lost, the highest percentage of protein metabolism observed in the entire series. As acetonuria diminishes and more calories are obtained from carbohydrate and from the more completely oxidized fat, protein metabolism diminishes. It has been the practice in this clinic to make the proportion of protein calories to total calories quite low in the initial diets (5 to 10 per cent). When the

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<sup>27</sup> Emery and Benedict. *Am J Physiol* **28** 301, 1911. These authors give a heat value of 4,323 calories per gram for pure glycerol.

(K') represents the number of millimols of ketogens completely oxidized. In the case of Walter A (Table 4), K'/A ranged in value from 0.9 to 2.5, and in the case of Charles G (Table 8), K'/A varied from 0.9 to 1.8. Even at the point of disappearance of ketonuria in the case of Walter A (Table 4), the ratio of K'/A was 1.7:1.

#### RESULTS OF DIET REGULATION

The plan has been to cover the maintenance requirement of every patient with a diet low in protein, at first, containing the proportion of at least one molecule of antiketogenic substance to each molecule of ketogenic substance in the diet. Four of the five patients described in this report have shown rapid and marked improvement. The failure of one case in five represents an unduly high proportion of failures to the total number of cases treated in this way (about 100 cases). A separate report of the whole series will be made, which will give an idea of the general results achieved.

Regarding Case 4, in which treatment by this method was unsuccessful, it was recognized from his previous history and from his record after leaving this clinic that he could have been rendered sugar free by starvation. It was never possible to keep him sugar free on a maintenance diet. The patient was already in such an emaciated condition and in such constant suffering from hunger that it was not believed to be justifiable to increase his suffering by a futile starvation treatment. Specific insulin therapy need not be further discussed in this case than to state that the insulin at that time was not potent in the amounts available.

There were several temporary departures from the general plan of treatment in these cases. Days on which only green vegetables were eaten were occasionally interpolated and were usually found to hasten the cessation of glycosuria. In diabetic patients who were overweight it was sometimes found to be advantageous to furnish only the protein and carbohydrate in the amounts calculated for a maintenance diet, causing the patient to burn body fat. Reduction in weight in this way is easy and beneficial. Of our present series of five cases, none of the patients was overweight, so that this procedure will be best illustrated in a report of the whole series.

The substitution of an equal amount of glycerol for the calculated amount of carbohydrate in the diet is often of value in reducing glycosuria, and especially in reducing ketonuria. Such a result is well illustrated in Case 3, Charles G. Cremer.<sup>26</sup> He studied the conversion of glycerol into sugar. In his experiments on phlorrhizinized dogs the sugar excreted in excess of the maximum D:N ratio of 3.65 represented only

<sup>26</sup> Cremer, C. G. *Physiologie des Glycogens, Ergebn. d. Physiol.* **1**: 888, 1902. The work of Kulz and von Mering is quoted and an extensive bibliography is given.

# SOME INTERESTING CASES OF CALCAREOUS DEGENERATION FOUND IN THE THORAX

J S PRITCHARD, M D

BATTLE CREEK, MICH

Before considering the following cases of calcareous degeneration found in the thoracic region, a brief review of the subject seems advisable. The chemical, physical and clinical evidences of pathologic calcifications have been noted from time to time for many years, interesting cases have been reported in the literature and important treatises written regarding cause and effect.

Aristotle and Galien<sup>1</sup> mentioned cases of "stone in the lung" in their records. Sommering<sup>2</sup> in 1769 wrote of a case of pulmonary calcification which he considered as a secondary manifestation (metastasis). In 1824, Rullier<sup>3</sup> reported a case of primary calcification of a right upper lung in which a great number of calcified fragments were found. Fuhmann<sup>4</sup> thought that the deposition of calcium salts might follow any chronic irritation of the body tissues, and that this explanation accounted for "exercise bone" (calcium formation in deltoid muscle) and "the riders' bones," which proved to be calcium deposits in the adductor muscles of the thigh of persons subjected to prolonged irritation due to horseback riding. Years ago Morton<sup>5</sup> found a special type of consumption which he termed "stony phthisis" on account of the frequent occurrence of stonelike deposits in the expectoration of a patient suffering from the pulmonary form of the disease. In 1858, Virchow wrote extensively on this subject and described necropsy evidence of calcium deposits in the lungs, stomach, kidneys, intestines and blood vessels.

Two types of calcification have been described, the morbid, which follows definite pathologic changes, and the type which might be termed physiologic and which we often find among the manifestations of senility.

The cause of calcareous degeneration has been the subject of much splendid experimental investigation, and in summarizing the probable factors one is impressed by the fact that no specific cause can account for this form of degeneration, that a number of condi-

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1 Aristotle and Galien, quoted by Fiozzì, F. Sopra un caso di calcolosi polmonare, *Gazz. med. de Roma* **38** 562, 1912.

2 Sommering, quoted by Osslan, R. Contributo all studio dell' ossificazione del pulmone, *Riv. osp.*, 1913, p. 111-337.

3 Rullier, quoted by Osslan, R. Footnote 2.

4 Fuhmann. Ueber einen Fall von pleuritis calculosa, München, 1908.

5 Morton, quoted by Fiozzì, F. Footnote 1.

patient's protein metabolism has reached its minimum, the protein of the food should be increased slowly to attempt to establish nitrogen balance at as low a level as possible (15 per cent of the total number of calories or less)

By the use of the methods of diet adjustment illustrated in the preceding five cases, it has been found possible to render the vast majority of diabetic patients sugar free without reducing the diet below the maintenance requirement. The disappearance of sugar from the urine is not so rapidly accomplished as by the use of starvation. However, it is believed that if one takes into account the time required in slow building up of the diet after starvation, that time is saved in getting patients to utilize adequate diets. Not only is time saved, but much suffering on the part of the patient is avoided.

Some patients cannot be rendered free from glycosuria by these methods. With such patients, diet restriction is futile in the absence of other means of increasing carbohydrate utilization. Fortunately, the means of accomplishing this are at hand in insulin. Case I received treatment with insulin for a short time.

Discussion of the therapeutic use of insulin will be reserved for a later publication. In the series of insulin treated cases the diets were adjusted in the manner described here, so that the patients of this series will serve to a certain extent as controls to those of the insulin series.

#### SUMMARY AND CONCLUSIONS

1 Calculations of the ketogenic-antiketogenic balance from the foodstuffs actually metabolized in diabetic subjects show that a maximum of one molecule of antiketogenic substance is required for the complete oxidation of one molecule of ketogenic substance. Frequently less than one molecule of antiketogens will suffice.

2 The records of five patients serve to illustrate both successes and failures of a method of diet adjustment, the aim of which was to afford each patient (a) at least enough calories to cover the maintenance requirement for rest in bed (basal metabolism plus 10 per cent), (b) to reduce the level of protein metabolism by means of a low protein intake, (c) to give the foodstuffs in such proportions that at least one molecule of antiketogenic substance will be available for every molecule of ketogen formed.

3 The substitution of glycerol for carbohydrate is a successful means of combating ketosis in certain cases.

4 The improvement noted in patients to whose diet calcium and phosphorus were added (as  $\text{Ca}_3[\text{PO}_4]_2$ , calcium hexose phosphate, and calcium glycerophosphate) is not attributed to the effect of this addition.

Important studies regarding etiology were made by Heller and Stade<sup>11</sup> who, however, reached no final verdict from the consideration of many cases from the standpoint of occupation, age and sex, chemical studies as well, failed to reveal anything definite which could be regarded as a probable cause. Aschoff<sup>12</sup> believed that some organic substances like hyalin or fibrin had an affinity for calcium and that the presence of these was necessary for the early formation of calcification.

Gideon Wells<sup>13</sup> published several articles on this phenomenon, and his splendid Harvey lecture is a most complete essay on research in this field. Among many important conclusions he showed that the deposits of lime salts were similar in physiologic and pathologic processes, and that frank calcification might occur in the absence of a definable pathologic etiology. He concluded that the process was possibly a calcification of protein substances which have an elective choice for lime salts and that such a phenomenon was not a chemical reaction. He also showed clearly that such changes were found in rickets, osteomalacia and osteoporosis, thus the chemical and the physical behavior of calcification are important in the solution of questions pertaining to regeneration and repair of bone. Wells emphasized the distinction between calcification and ossification, and later showed that a soft, foreign substance, like gelatin, would cause the precipitation of lime salts.

Von Kossa<sup>14</sup> believed that a diet rich in calcium should be considered as a cause of calcification and proved by animal experiments that food rich in lime caused calcium deposits in the kidneys of the treated animal.

Hueck<sup>15</sup> who has studied this subject extensively, stated that his observations led him to conclude that calcification is not connected with any particular process or disease.

Metastatic calcification occurs in many instances. Askanazy<sup>16</sup> reported that twenty-nine cases in the literature show calcium deposits in healthy tissue of the lungs, kidneys or gastro-intestinal tract. Of

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11 Heller and Stade, quoted by Hueck. *Centralbl f allg Path u path Anat* **24** 4.

12 Aschoff, quoted by Hueck. Footnote 11.

13 Wells, H. G. Calcification and Ossification, *Arch Int Med* **7** 72 (June) 1911.

14 Von Kossa. Ueber die im Organismus kunstlicherweise erzeugten Verkalkung, *Beitr z path Anat u z allg Path* **29** 163 1901.

15 Hueck. Ueber Verkalkung von Alveolarepithelien. *Centralbl f allg Path u path Anat* **24** 4, 1913.

16 Askanazy. Beiträge zu Knochenpathologie. *Festschr f Jaffe, Burns wick*, 1901.

tions are accountable for abnormal calcareous deposits in the various body tissues is apparent. The most striking conclusion concerning the etiology of this phenomenon is that any chronic irritation, either chemical, mechanical or infectious, may cause a pathologic calcareous degeneration of the tissues involved. Necrosis and suppuration are a common predisposing factor in deposits of calcium salts, especially in the pleura.

Virchow thought that the phenomenon of calcification was due to a superabundance of calcium salts in the blood and that inadequate kidney elimination might also be a causative factor, as many of his cases were associated with advanced renal disease. Virchow believed, too, that the deposits occurred more frequently in organs rich in blood supply, he also made the interesting, and since proved accurate, observation that many cases of pulmonary calcification were associated with destructive bone lesions.

Chiari,<sup>6</sup> a few years after Virchow made his observations, found extensive lime deposits in the lungs without any changes in the osseous structures. Kischenski<sup>7</sup> came to similar conclusions later. In the late seventies Litten<sup>8</sup> advanced the theory that, in the formation of calcareous deposits in the kidneys, one or more irritants acted on certain tissues, like the tubules, and caused an induration of the epithelium followed by a degeneration of the protoplasm. This affected area had an affinity for lime salts carried to it by the blood and lymph.

By experiments on animals, Leik<sup>9</sup> showed that the amount and velocity of the blood supply to the tissues had some bearing on the subject of calcification, he also demonstrated that it was possible to obtain bone formation in the pelvis of the kidney in a rabbit by ligating the renal artery, the calcification occurring in the kidney from sixteen to twenty days later. He wrapped the kidney with omentum and thus established a collateral circulation, if this were not done, three months' time was required to produce calcification. In other words, change in the amount, force or rate of flow of blood supplied to the part was a causative factor in calcareous degeneration. Von Recklinghausen<sup>10</sup> also showed that calcification occurred in tissues poor in blood supply and that this process could proceed when the calcium content of the blood was normal.

<sup>6</sup> Chiari. *Wien med Wchnschr* **1**, 1878.

<sup>7</sup> Kischenski. *Ueber Kalkablagerung in den Lungen und im Magen*. *Med Oborcy, Dez*, 1900.

<sup>8</sup> Litten. *Ztschr f klin Med* 1879.

<sup>9</sup> Leik. *Heteroplastische Knochenbildung in Nieren*, *Arch f klin Chir* **85** 118, 1908.

<sup>10</sup> Von Recklinghausen quoted by Klotz. *Exper*, 1905, p 633.

By injecting mercuric chlorid into the kidney substance of a rabbit, Tartarini-Galleani<sup>25</sup> produced a lesion which showed signs of calcification after undergoing fibrosis and necrosis

*Distomum pulmonale* has been described as a cause of pulmonary calcification by Koehler<sup>26</sup>

Hess<sup>27</sup> points out that hygienic surroundings plus the addition of sunlight and fresh air, as well as diet, are important influences in the prevention and cure of rickets. The production of rickets in mice through a deficient supply of actinic rays suggests the presence of the definite influence of sunshine on the process of calcification

In summarizing the evidence as to the cause of calcareous degeneration, the following points may reasonably be considered as having some etiologic bearing

1 Any irritant to the tissues, either mechanical, chemical or infectious, the latter being a most important factor in the cases presented in this article

2 Any condition which lowers the vitality of the organism

3 Changes in the composition, velocity or volume of the blood

4 Interference with the general or local nutrition

5 The questionable effect of blood and tissue chemistry

6 Poor assimilation or deficient metabolism of the involved tissues

7 Constitutional conditions affecting the general metabolism

8 Any disease of the osseous system which may cause the liberation of lime salts

9 Alterations in the tissues which cause retention of chronic irritants, such as necrosis, suppurations, chronic inflammatory changes or traumatism

10 Special selective power of certain tissues for lime salts

11 The effect of sunlight on the body tissues and metabolism. The production of rickets in mice through deficient supply of actinic rays suggests the presence of a definite influence of sunlight on the process of calcification

12 Vasomotor disturbances

13 Possible influences of endocrine derangements

14 Variations in the carbon dioxide blood content

15 Hemorrhage into the tissues

25 Tartarini-Galleani. *Sperimentale* 58 371, 1904

26 Koehler, Alban. *Grenzen des normalen und Anfaenge des pathologischen in Roentgenbilde*, Ed 3, p 131

27 Hess, A. F. *Newer Aspects of the Rickets Problem*, J A M A 78 1177 (April 22) 1922



this number, all but four cases showed definite destructive bone disease`

Hofmeister and Tanaka<sup>17</sup> caused extensive calcium metastases in the lungs, stomachs and kidneys of rabbits by intraperitoneal injections of soluble calcium salts. These authors called attention to the fact that the organs in which the metastases occurred were also the chief organs which excrete acid. Kalase<sup>18</sup> made similar experiments and came to the same conclusions concerning the metastases in the kidneys, lungs and stomach caused by intraperitoneal injections of soluble calcium salts.

The idea that some endocrine disturbance might be of etiologic significance was propounded by Harbitz<sup>19</sup>. He mentions two kinds of pulmonary calcification, the type following bone lesions (metastasis) and a primary variety not associated with any osseous degeneration.

An interesting case of pulmonary calcium metastasis is reported by A. W. Crane<sup>20</sup>. Here the lung calcification was the remote result of a primary carcinoma of the prostate with malignant metastasis in the pelvic bones. The disintegration of the pelvic osseous tissue liberated lime salts, which in turn formed a calcium metastasis throughout both lungs.

Deficient nutrition of the tissues was also shown by Borst<sup>21</sup> to result in the deposit of calcium, and this was increased when the tissues were deficient in eliminative powers.

Von Werra<sup>22</sup> made an important contribution to the subject when he showed that experimentally produced calcium in the kidneys of rabbits was sometimes reabsorbed in a few weeks. Maximow<sup>23</sup> proved that such deposits may last a year and then disappear even after secondary ossification has taken place. This brings up the question as to whether or not in our clinical observations we are justified in always considering localized concretions as obsolete. Dunham<sup>24</sup> found that calcified nodules in the lung roots may possess definite caseous centers and that for this reason such pathologic changes should not always be considered as evidence of an obsolete tuberculosis.

17 Hofmeister and Tanaka, quoted by Wells. Footnote 13

18 Kalase. Beitr. path. Anat. u. z. allg. Path. **7** 516, 1914

19 Harbitz, Francis. Extensive Calcification of the Lungs as a Distinct Disease, Arch. Int. Med. **21** 139 (Jan.) 1918

20 Crane, A. W. Pulmonary Metastasis, Am. J. Roentgenol. **5** 479, 1918

21 Borst. Die Lehre von den Geschwulsten, vol. 1

22 Von Werra. Ueber die Folgen des vorübergehenden und dauernden Verschlusses der Nierenarterie, Virchows Arch. f. path. Anat. **88** 197, 1882

23 Maximow. Ueber experimentelle Erzeugung von Knochenmarkgewebe. Anat. Anz. **28** 609, 1906

24 Dunham. Wisconsin State M. J., July, 1921

The ribs and costal cartilages have long been the subject of considerable comment. Calcification of any or all of these has been often mentioned as a suggestive sign of early pulmonary tuberculosis and has also been considered as evidence of a predisposition to the disease. Martins and Lorey<sup>33</sup> believe that the phthisical chest form characterized by the long, flat and slender thorax and the steeply descending ribs, together with an ossification of the first rib, is by no means rare in the tuberculous. Freund, about fifty years prior to this, called attention to the narrowing of the thoracic inlet and its probable association with tuberculosis.

At the Battle Creek Sanitarium Clinic, the author has attempted to make a study of calcification of the thoracic cage. In a series of over 7,000 cases the following has been the routine procedure. At the time of the physical examination of the chest a careful history was taken, the laboratory findings included a Wassermann test, in each case stereoscopic chest plates were secured, which were interpreted by the writer in conjunction with the clinical study, the final opinion was based on a summary of the whole investigation. In this way an opportunity was presented for the study of a large number of roentgen-ray stereoscopic photographs of the chest, nevertheless, it is with considerable hesitancy that any opinion is offered concerning the significance of calcium deposits in the ribs, cartilages or sternum.

From the foregoing study, however, a few points present themselves which may be of some importance. First, the number of cases with frank lesions in the upper portion of the lungs, active or inactive, which show no definite sign of calcification in the thoracic cage is remarkable. Second, extensive calcification of the ribs or cartilages occurs frequently without any pulmonary disease. Third, the long, thin, flat, narrow thorax may be more prone to calcification of the upper anterior part, but in my series I have found a considerable number of calcified deposits in all forms and types of the adult thorax.

In gastric calcification, Hofmeister<sup>34</sup> showed that the interglandular tissue in the upper part of the fundus was the usual location, and he emphasized the fact that the acid secreting glands were also situated in this region.

The pleura is not an uncommon seat of frank calcareous deposits, and it is not difficult to find many references on this in the literature. Empyema, extensive and localized, is perhaps the most important cause, as a rule, these deposits take the form of plaques or platelets. The lower half of the pleural cavity is the more common location when the

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33 Martins, F, and Lorey, Alex., in Brauer, Schroder, Blumenfeldt. *Handbuch der Tuberculose* 1, p 726

34 Hofmeister. *Ergebn d Physiol* 9 429, 1910

## 16 Factors influencing osmosis

17 After all theories have been propounded, there still remain a goodly number of cases of calcareous degeneration unexplained from the etiologic standpoint

Few, if any, types of body tissues are immune to calcareous degeneration. After a careful study of the literature, the writer concluded that the peritoneum was perhaps one of the tissues least affected.

Chiari found calcareous deposits in the ampulla of the spermatic cord and in the parietal lobe of the brain. Paton reported a case of extensive calcification lining the walls of a necrosed mass between the pleura and the pericardium in a man 70 years of age. Heuer<sup>28</sup> described an unusual case of a large triangular mass in the right pleural cavity of a patient aged 53. The base of this mass rested on the diaphragm, and the walls contained extensive shell-like calcareous plates, the contents were air and fluid. Pathologic examination gave no specific information except that it was a calcified mass.

L. E. Brown<sup>29</sup> records two interesting cases of lung stones and considered that it was a question whether or not pneumoliths, bronchololiths or lung stones were a clinical entity. He emphasized the importance of the bronchoscope and roentgen ray in diagnosis. Frozzi<sup>1</sup> cites a case of lung stone in an Italian girl aged 18. He could not agree with Gallippe or Rosenberg in their theory on etiology (salivary lithiasis). Helbig<sup>30</sup> concluded that lung stone was a comparatively rare disease, and up to the time of his publication found few cases reported in the literature.

Canio<sup>31</sup> described a case of pulmonary calcification which came to necropsy as the result of a chronic dysentery. This is of interest on account of a similar case reported in this article, in which an extensive pulmonary calcification was associated with diarrhea. Kochel<sup>32</sup> made a study of the pulmonary tissue involved in this phenomenon and concluded that the alveolar epithelium was free from deposits.

The more frequent locations in which lime deposits make their appearance are undoubtedly the lungs, pleura, gastric and intestinal regions, the blood vessels, glands, joints, tendons, cartilages and bursae. The peritoneum is perhaps less frequently affected.

28 Heuer. Bull. Johns Hopkins Hosp., April, 1917, p. 153.

29 Brown, L. E. Pneumoliths and reports of Cases, Cleveland M. J. 16 21, 1917.

30 Helbig, M. Munchen med. Wchnschr., October, 1916.

31 Canio, J. Analyse chimique de deux calculs pulmonaire trouve a l'autopsie d'un malade mort de dysenterie chronique, Rev. med. d'Afrique du Nord 7 61, 1904.

32 Kochel. Ueber Kalkinkrustation des Lungengewebes, Deutsch. Arch. f. klin. Med. 64, 1899.

process underlying calcification. In a splendid experimental study, he showed that this process was, in all instances, preceded by the deposit of a soapy material which existed in the chronically inflamed tissues. This substance seemed to act as an attraction for the ultimate deposit of lime salts, and as the latter increased the former disappeared.

Wells quotes the interesting theory advanced by Murray and Irving<sup>48</sup> concerning the lime formations in coral reefs, the hypothesis being that the calcium is formed by the action of the sea water, which contains soluble calcium sulphate and ammonia carbonate. The latter

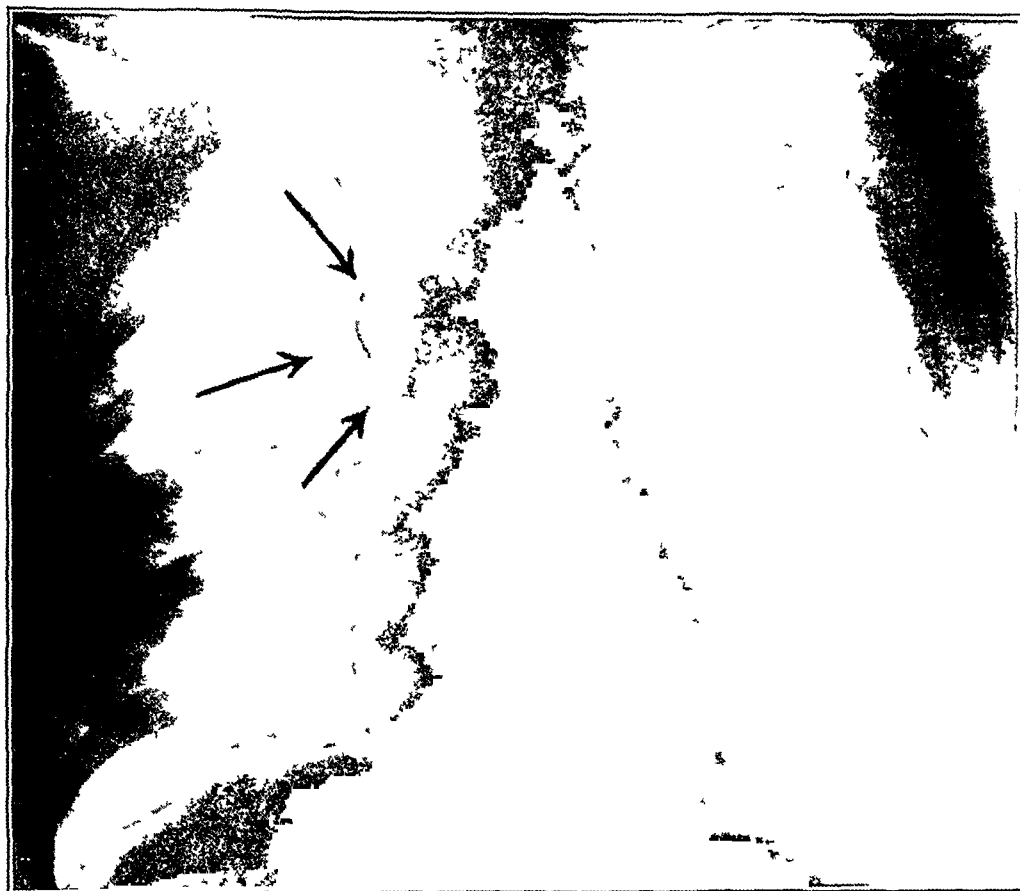


Fig 1 (Case 1) —Numerous "lung stones" varying in size from that of grains of sand to that of large peas, have been expectorated on five different occasions. After this occurrence, the mass disappears until a redeposit of lime salts occurs in the glandular tissue.

was formed by the metabolism of animal life causing a precipitation of the calcium carbonate. Brown's<sup>29</sup> chemical analysis of the pneumoliths found in his cases shows about the average proportion of phosphate and carbonate as compared with many other estimates. Chemically these concretions were found to contain the following proportions of the ingredients: calcium phosphate, 1.56, calcium carbonate, 0.39, magnesium carbonate, 0.05, and soluble fats, 0.06.

pathologic process is extensive, small plaques are found in the middle third of the horizontal plane, while apical patches are not so common except when associated with pulmonary calcification. The clinical history of the case suggests that most of the pleural calcifications are probably not due to the action of the tubercle bacilli. In most cases found in my work, no history of present or past tuberculosis could be elicited, but a definite period of illness associated with what the patient called pleurisy, lung fever or pneumonia was usually admitted—suggesting a nontuberculous infection. Since 1800, the literature mentions many authors who described pleural calcification. Those cases described before the advent of the roentgen ray were, in most instances, mentioned in necropsy reports, death being due to other causes. The roentgen ray has led to an increase in the number of such cases reported.

Among the many authors who have written on the subject of calcium deposits in the pleura, I shall call attention to a few of the more recent, such as Courmont and Tixier,<sup>35</sup> Gabszewicz,<sup>36</sup> Todaro,<sup>37</sup> Sweet,<sup>38</sup> Goulliond,<sup>39</sup> West,<sup>40</sup> Huguen,<sup>41</sup> D'Agata.<sup>42</sup>

The composition of calcareous deposits, especially those found in the glands and arteries, was described by Moore and Williams<sup>43</sup> and the various forms of calcification and ossification were discussed by Moschowitz<sup>44</sup> in 1913. Posharissky<sup>45</sup> found that in twenty-eight cases of lung concretions there was evidence of ossification in seventeen, or 60 per cent, while Darbois<sup>46</sup> thought that the tubercle bacillus was the cause of most pulmonary concretions. Kochel found it difficult to establish the lime content of some protein combinations, such as the products of healthy coagulation and hyaline tissue.

Klotz<sup>47</sup> states that, while much has been written on this type of degeneration, little has been ventured in the explanation of the

35 Courmont, J, and Tixier. *Lyon méd* **103** 46, 1904

36 Gabszewicz. *Calcification of Pleura*, *Gaz lek* **26** 121, 1906

37 Todaro, N. *Calcificazioni plurale come esoto do pleurite*, *Cronica suppurativa comire San Milano*, **19** 369, 1908

38 Sweet, W S. *Calcification of the Pleura and Empyema*, *Brit M J* **1** 17, 1911

39 Goulliond. *Resection d'une large plaque calcaire d'origine pleurale*, *Lyon med* **107** 350, 1906

40 West, Samuel. *Tr Clin Soc London*, **39** 42, 1906

41 Huguen. *Etude anatomique des inflammations chronique des sersuses et de leur effet sur les organes qu'elles recouvrent*, *Geneve*, 1903, p 47

42 D'Agata, G. *Empyema chronica con calcificazione pleurale*, *Clin Milano*, **23** 24, 1915

43 Moore and Williams. *Liverpool M Clin* **27** 157, 1912

44 Moschowitz. *Proc New York Path Soc* **13** 19, 1913

45 Posharissky. *Beitr z path Anat u z allg Path* **38** 135, 1905

46 Darbois, P. *Les calcifications pleura-pulmonaires*, *Bull et mem Soc radiol med de France* **6** 60, 1914

47 Klotz, Oskar. *J Exper Med* 1905, p 633

the value of this method in locating concretions in the lungs, as the roentgen-ray examination was the only method which revealed such a pathologic condition in the three cases cited by him

Few symptoms occur in the pathologic formation of lime salts Osslan<sup>2</sup> points out that calcification and ossification frequently occur in the pulmonary substance without causing any clinical manifestations Brown<sup>29</sup> called attention to the fact that the foreign body action of

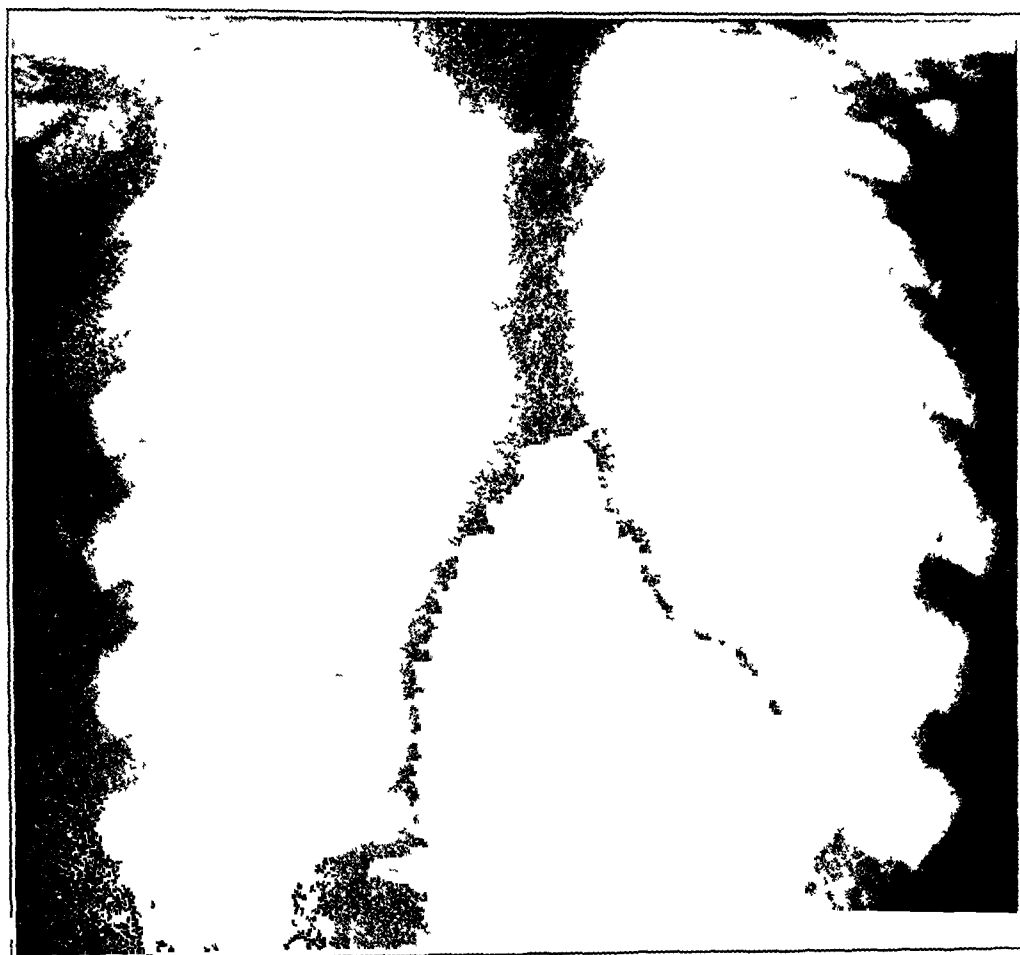


Fig 3 (Case 3) —The same solid glandular formation in the upper right lung root as seen in Figure 2 There was no history of any past respiratory disturbance which could account for this condition

pneumoliths must be considered when the symptomology is considered The concretions form erosions of the bronchi and lung tissue, and the organized infections or abscesses which follow cause the characteristic symptoms of a foreign body The clinical symptoms, then, depend on the mechanical behavior of the concretions, the possibility of associated infection, their size and location, whether loose or impacted

In similar lung or pleural affections, the physical findings vary according to the amount and type of the original pathologic process

The diagnosis of pathologic deposit of calcium was seldom made before necropsy, prior to the advent of the roentgen rays. Occasionally, the grating of a knife or needle coming into contact with a calcified area is the first intimation of the possible existence of such a condition. The history of some past chronic inflammatory process, especially when accompanied by tissue destruction and necrosis, sug-

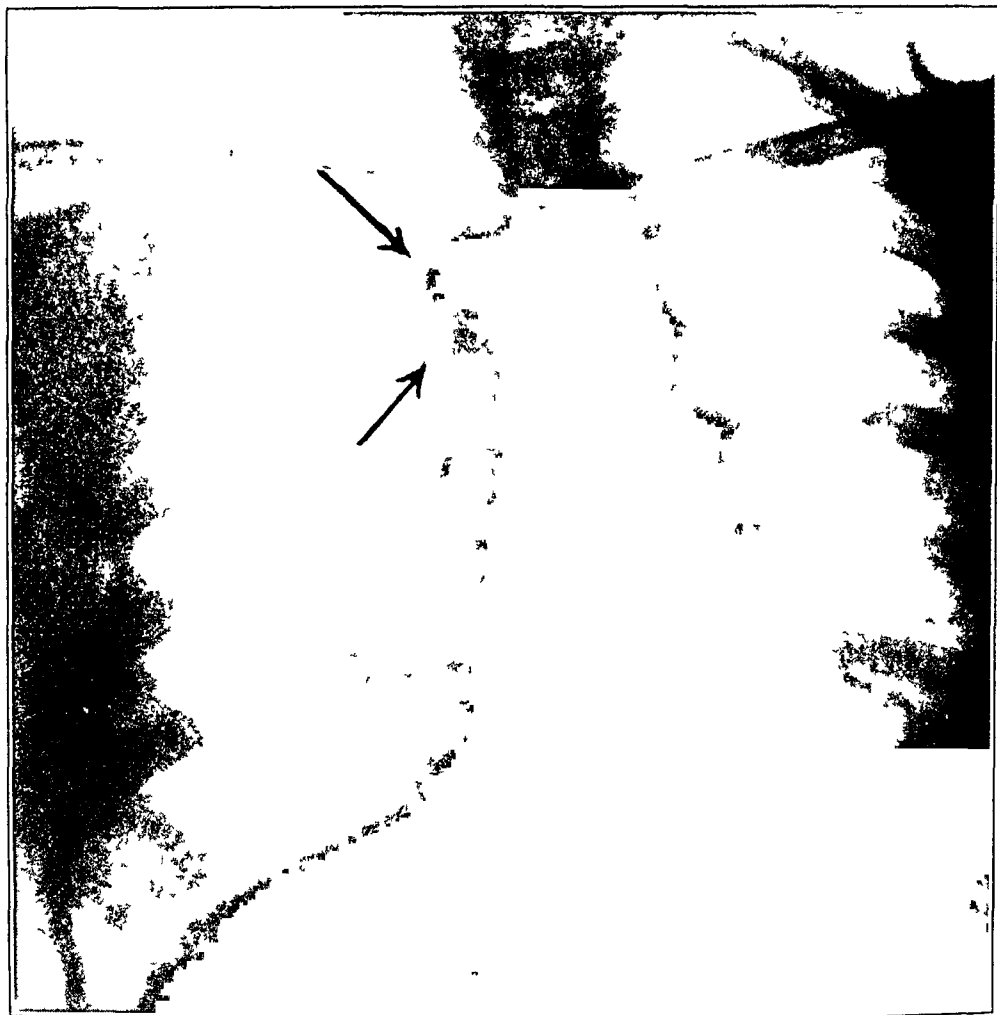


Fig 2 (Case 2)—Calcified bronchial gland. In this case there was no history of "lung stones."

gests the possibility of some deposits of calcium. This is most reasonably assumed in pleural and pulmonary affections.

Roentgenology has proved the most important help in the diagnosis of this process. The dense, hard, concrete, clean-cut shadow caused by this particular formation is characteristic. Infroit<sup>49</sup> emphasized

<sup>49</sup> Infroit. Concretions calcaires du pumon simulant a la radiographie des eclats d'obus, Bull et mem Soc anat de Paris 89 337, 1919.

attacks of cough and slight fever accompanied by expectoration of numerous gravel-like substances which proved to be lime salts deposits. These deposits varied in size from that of fine sand to that of large peas. During the interval between the attacks, which seldom lasted more than a week, the patient was troubled with a slight bronchitis. She was sent to me during one of these attacks, and the following notations were made:

There was definite goiter of long standing, but no evidence of hyperthyroidism, the basal metabolism was plus 6, nutrition and development were normal. She had a severe cough followed by the expulsion at intervals of small calcareous granules, irregular in formation. There were no acid-fast

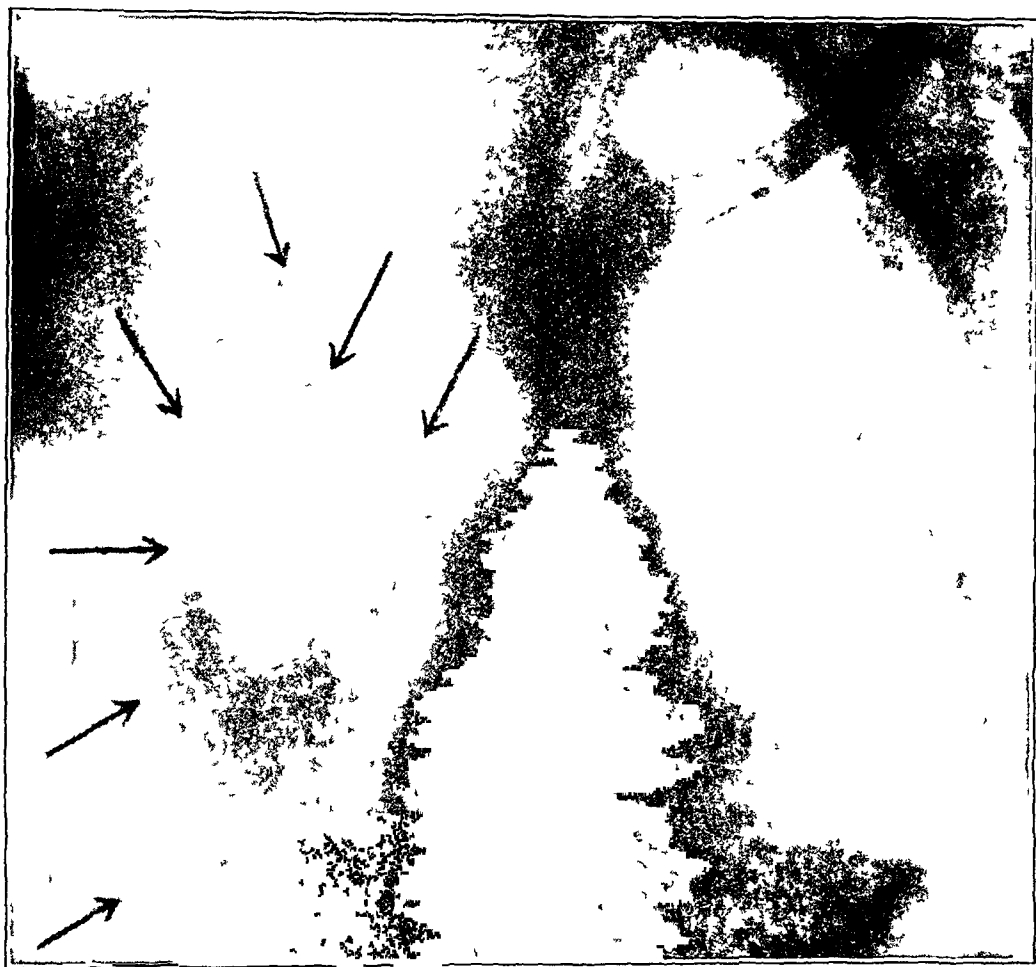


Fig 5 (Case 5) —An extensive calcification of the right pleura showing a definite compression of the lung tissue. The patient was 83 years of age and gave a history of pneumonia and empyema fifty-nine years ago. He has enjoyed reasonably good health ever since.

bacilli in the sputum. There was slightly impaired resonance over each lung root in front, with increased intensified voice sounds and a few fine râles in the left interscapular region.

The stereoroentgenograms (Fig 1) showed a peculiar round, mulberry-shaped shadow below the inner half of the right clavicle in the upper lung root zone. The contents suggested an irregular mass of calcareous degeneration. The mass had the appearance of a large calcareous gland which communicated with some of the larger bronchi and was the source of the "lung stones" expectorated at intervals.



The breath sounds and percussion note may be altered, as we find in any fibrosis. This may or may not be associated with a sign of a chronic bronchitis. The physical findings seldom give us much information in the diagnosis of calcium concretions in the chest. The deposit of lime salts is not necessarily a part of a healing or healed process.

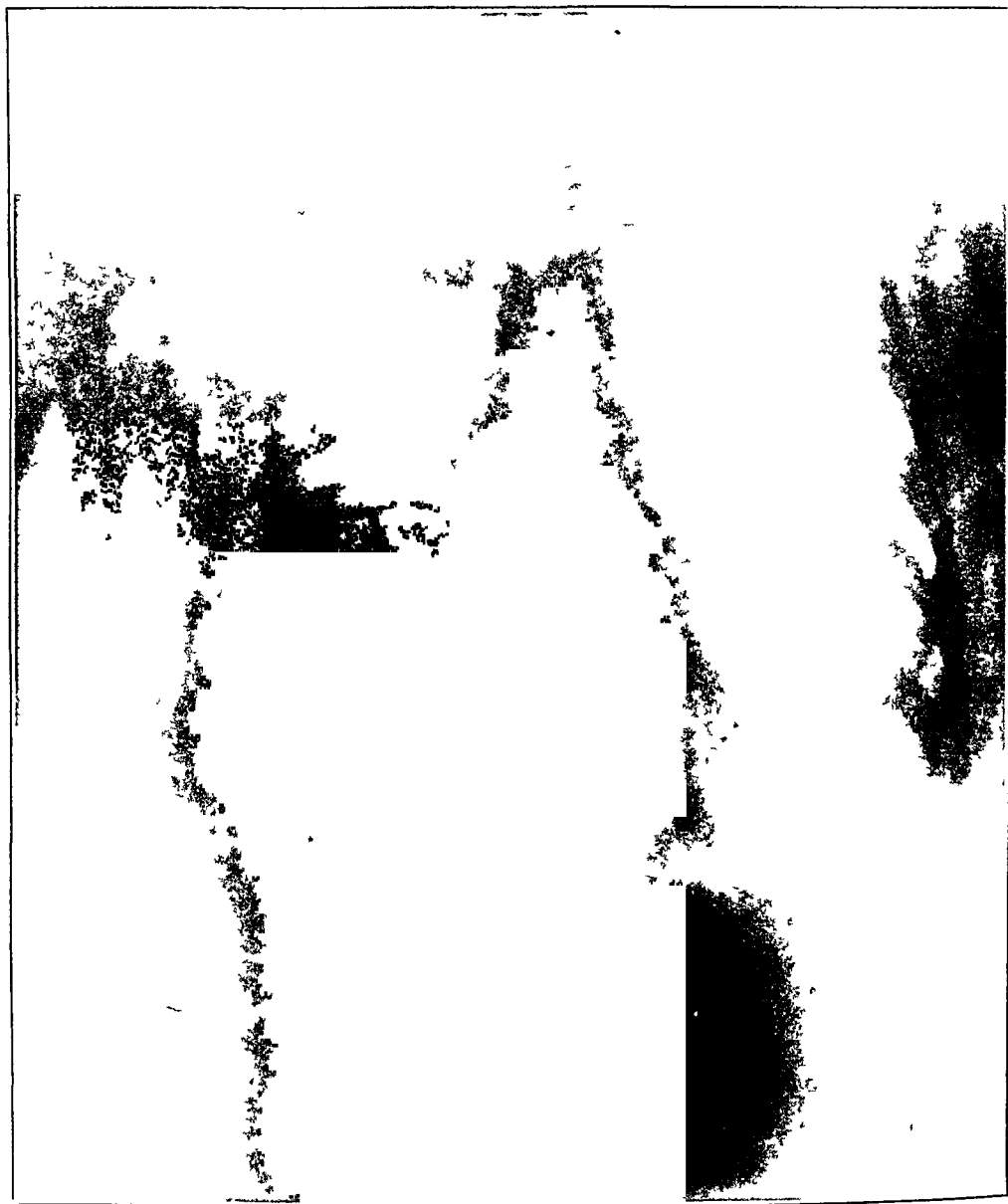


Fig 4 (Case 4)—An extensive calcification of the right pleura extending from the second rib in front to the base and horizontally to the posterior axillary line. There are definite calcium deposits in the upper part of each lung. This patient expectorated more than forty small irregular calcium concretions during a recent attack of bronchitis.

#### REPORT OF CASES

CASE 1—Miss K, 38 years old, a graduate nurse, gave a history of questionable typhoid at the age of 25 years, and, for the last six years intermittent

CASE 3—Mrs U W, shown in Figure 3, had practically the same type of case as the patient in Case 2. There were no respiratory symptoms and no history of any past respiratory disturbances, the patient was in normal health, and the enlarged calcareous glandular mass caused no symptoms.

CASE 4—Mrs C J was referred to my medical division with the following history. At the age of 18 she had an attack of what was called typhoid, although no abdominal symptoms were present, no other similar cases occurred in the neighborhood at the time. This attack was followed by some acute respiratory symptoms, with fever and pain in the lower right thorax. Since then she had not been strong and had taken good care of herself, thinking she had weak lungs, although physicians would not say she had tuberculosis.



Fig 7 (Case 6)—This illustration shows the bullet lodged in the muscles of the posterior abdominal region of the right side.

Recently a slight dyspnea and a wheezing within the chest had been frequent and disturbing symptoms. The patient had seldom been free from a slight cough and expectoration, but tubercle bacilli had never been found in the sputum.

Examination showed a slightly enlarged thyroid, no tremor, she was fairly well nourished, the right clavicle was prominent, there was extreme retraction of the entire right thorax with immobility, Kronig's isthmus was nearly obliterated, there was decreased resonance over the lower two thirds of the right thorax, associated with feeble breath sounds and increased whispered voice sounds, harsh breath sounds were found below the left clavicle.

The stereoroentgenograms of the chest (Fig 4) revealed a definite retraction of the right thorax, intensified at the base, and an extensive thickening of the pleura, with the density typical of calcareous degeneration. This thickness

It is now eight years since we made this examination, and since then we have repeated the investigation each year, sometimes three and four times a year. Many stereoroentgenograms of the chest were secured and they have shown this gland or sac entirely empty on one occasion, other times, at varying degrees of fulness, from a few pebbles to the completely filled sac, such as is shown in Figure 1. The patient has continued her vocation during these years, and, except for an occasional attack of "lung stones," has enjoyed good health. It has never been proved that the patient had a manifest pulmonary tuberculosis, although it is reasonable to believe that a tuberculous bronchial adenitis was the initial cause of the subsequent calcareous degeneration.

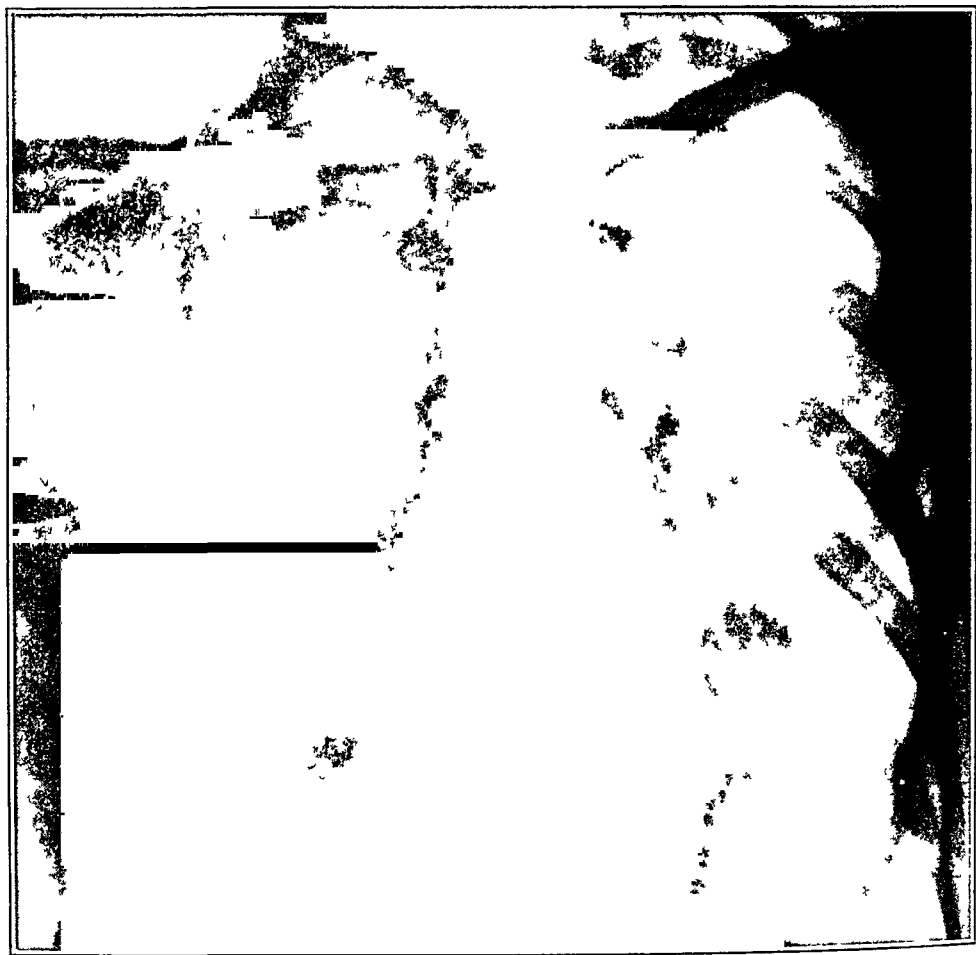


Fig 6 (Case 6)—The shadow in the right thorax is an organized mass (probably an organized hematoma) with a shell of calcareous deposits. Twelve years ago, the patient was accidentally shot in the right clavicle. The bullet traveled downward traversing the pleura and lodging below the right diaphragm.

CASE 2—Mrs. M. W., aged 49, had a severe bronchitis three years ago. She has no present respiratory symptoms.

Both physical and fluoroscopic examinations were negative. The stereoroentgenograms (Fig 2) showed a shadow similar to that described in Case 1 (Fig 1), characteristic of a calcareous mass the size of a walnut and corresponding in position to a bronchial gland (Fig 2). In this case, unlike Case 1, there was no history of the expectoration of "lung stones." Four years later this patient was reexamined and similar findings were noted.

The diagnosis was obsolete pulmonary tuberculosis, with extensive calcification of the right pleura and some calcareous degeneration in both upper pulmonary lobes

CASE 5—Mr A, aged 83, sought help on account of a cough which had troubled him for three winters, but which disappeared during the summer months. A small amount of mucoid sputum accompanied the cough, dyspnea was not a prominent symptom, considering the patient's age. No acid-fast bacilli were found on frequent examinations of the sputum.

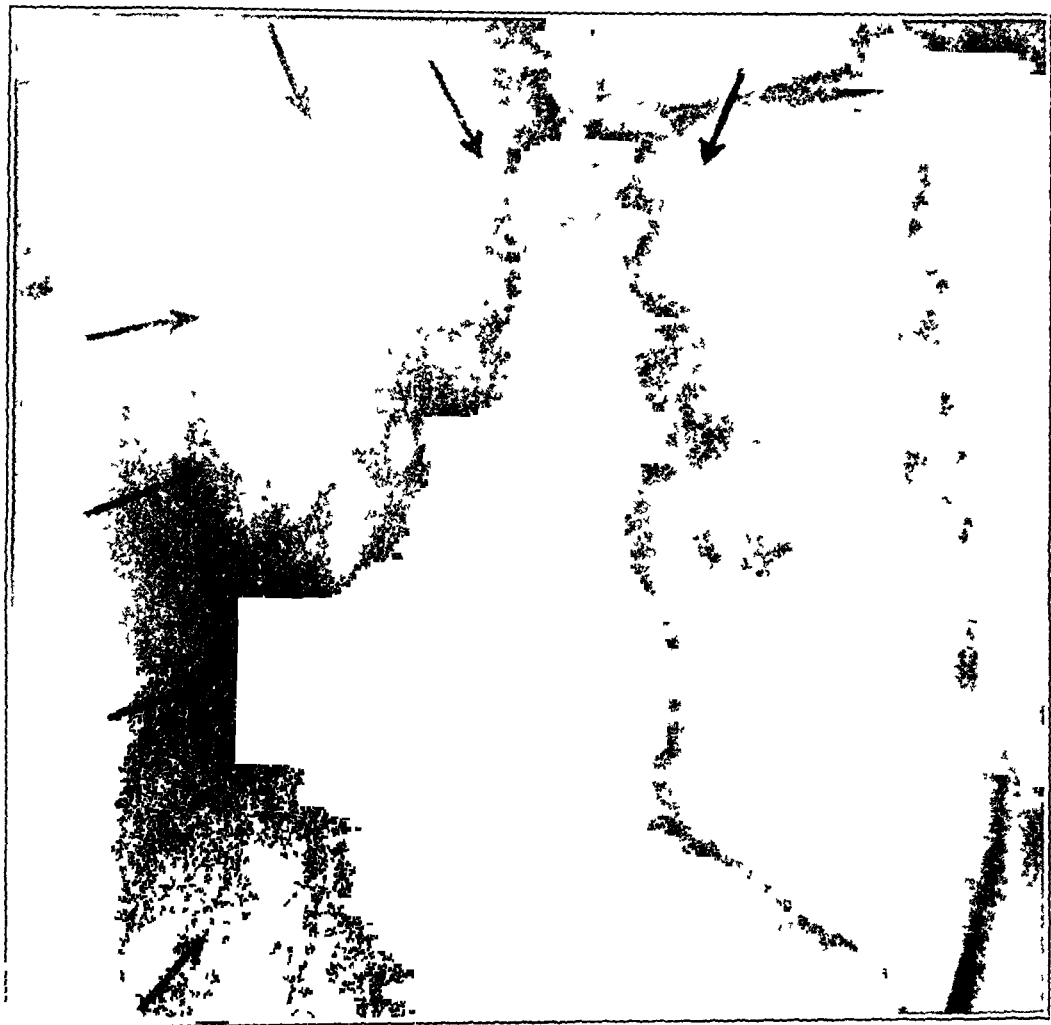


Fig 9 (Case 8)—This illustration shows an extensive calcified pleura in the form of a shell encasing the right lung. This patient had a severe and prolonged attack of pleurisy at the corresponding base forty years ago—a probable empyema following aspiration as the patient was confined to bed for four months following the latter.

The physical examination of the chest showed immobility of the right lower thorax and decidedly impaired resonance over the lower two thirds of the right lung. Auscultatory sounds were absent at the base, front and back, there were feeble breath sounds above the seventh rib in the back and the third rib in front, also a few fine râles at the base of the left lung in the axillary region.

In the stereoroentgenograms of the chest (Fig 5), a dense shadow was seen over the lower two thirds of the right lung, characteristic of a massive

began at the second rib in front and extended as low as the sixth, it was about 4 inches (10.16 cm) wide and held the lung in slight collapse. In the upper third of both lungs, there were some large calcareous deposits the size of beans. The right oblique chest plate showed no abnormal thickness or widening of the descending aorta.

The patient was referred to me two months later on account of severe cough and expectoration, the latter containing "lung stones" varying in size from small shot to a small pea, irregular in shape and rough in contour. This attack lasted three or four days, and during this time between forty and fifty of these calcareous substances were expectorated. On analysis, calcium car-

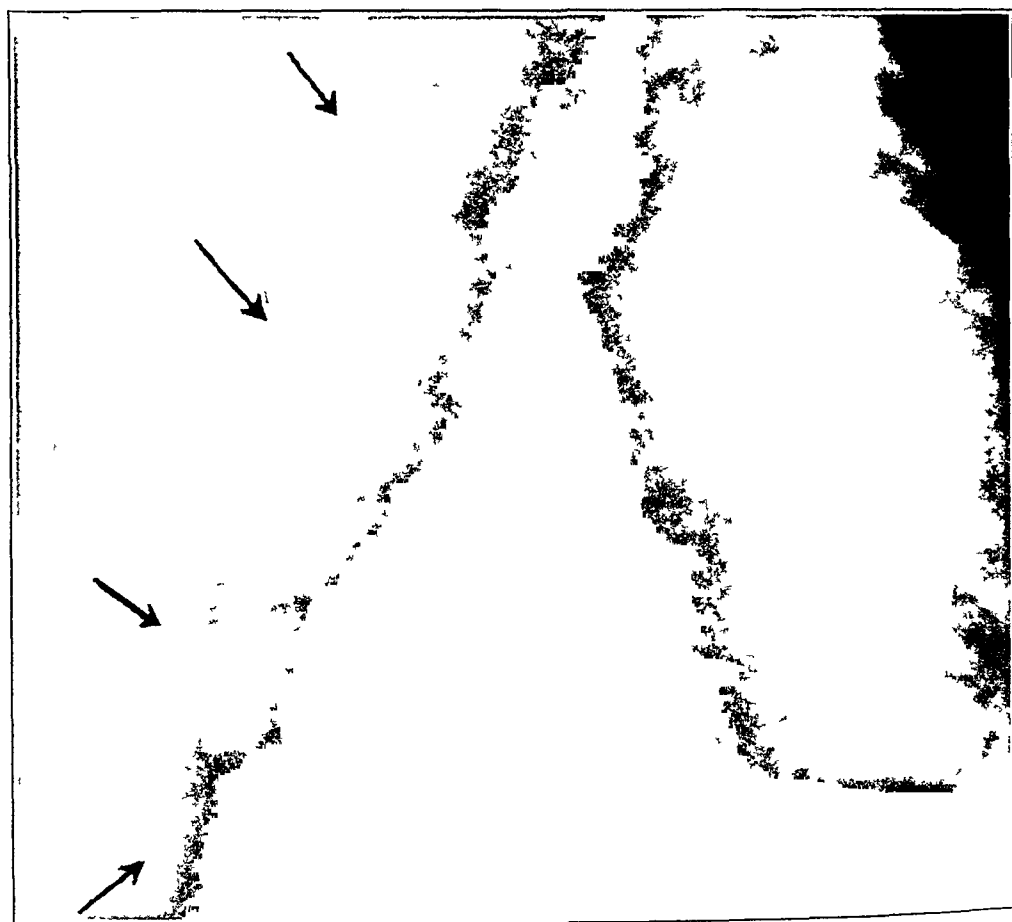


Fig 8 (Case 7) —The left lung is partially collapsed, and the pleura shows a dense fibrocalcareous thickening extending from the clavicle to the base. The patient sought advice on account of hypertension. There were no respiratory symptoms. A severe pleurisy in childhood was the only serious illness complained of.

bonate proved to be the chief ingredient, with about 6 per cent organic matter probably dried mucus. There were 93 gm of blood calcium in 100 cc of blood. The Wassermann test was negative. The intracutaneous tuberculin test gave a moderate reaction in twenty-four hours. A physical examination of the chest at this time revealed many medium sized râles, increased on coughing under the right clavicle to the fourth rib, in the suprascapular region, a similar condition was found on auscultation. It is our opinion that the disintegration of calcium deposits comes from the right thorax on account of the definite changes in the physical findings in two months' time.

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trouble, but recovered and has had no recurrence since. He sought treatment for gastrointestinal disturbances.

The physical examination of the chest revealed dulness from the clavicle to the base in the front of the right lung. Feeble breath sounds were present over the lower two thirds of the lung in the back. Stereoroentgenograms showed an extensive mass filling the pleural cavity, with a distinct calcified shell surrounding the mass (Fig 6). In all probability, the bullet (Fig 7) in its downward course caused an extensive hematoma, which afterward formed an organized mass with the deposit of calcium salts forming the outer border.

CASE 7—Mr C C H now aged 51 at the age of 16 was sick in bed for two weeks with a severe attack of pleurisy followed by two months of indisposition, at the age of 33, he had a severe attack of mumps, making a rapid recovery. Slight dyspnea had been a persistent symptom for years.

Physical examination of the chest showed the right lung to be clear. The left lung showed dulness from the clavicle to the base, with a great deal of

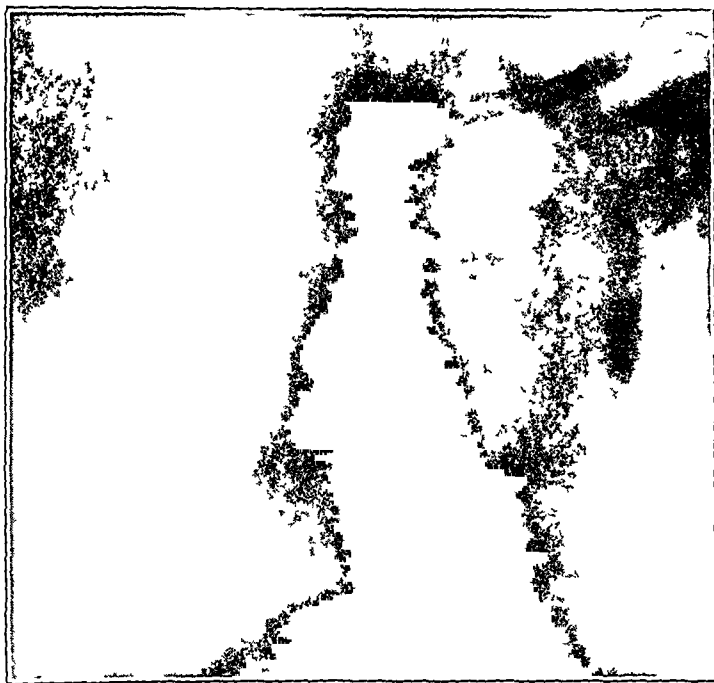


Fig 11 (Case 10)—This case is similar to that portrayed in Figure 10 except that the empyema occurred forty-three years ago.

retraction of the entire lung. Breath sounds were feeble. There were few crepitations in the first and second interspaces external to the midclavicular line. In the back, decreased resonance was found over the entire surface more intense from the sixth rib to the base. On auscultation feeble breath sounds and fine crepitations were heard at the base.

Stereoroentgenograms of the chest (Fig 8) revealed a long strip of fibro-calcareous tissue running from the clavicle to the base of the left lung. It is located about the outer third of the thoracic cavity and is about 2 or 3 cm in thickness, as viewed from the posterior-anterior position.

CASE 8—Mrs H G, aged 61 consulted a physician on account of symptoms characteristic of some circulatory disturbance. The history stated that forty years before, the patient had had a severe attack of pleurisy at the right pulmonary base, which necessitated the aspirating of considerable fluid. This illness kept the patient confined to bed for about four months with a moderate fever, cough and weakness. Later a sea voyage seemed to benefit her greatly.

shell of thickened pleura. The plates gave the suggestion of a lung encased in a cement jacket extending around the entire lower part of the lung.

The patient was given digitalis, and the cough slowly disappeared. It is now three years since we first observed this case, and the administration of digitalis each fall relieves the winter cough. The early history of this patient is interesting. During the Civil War, he enlisted in an infantry company and, after taking a forced march during a cold rain, was compelled to rest without shelter. Three days later, the patient was in the army hospital with a severe pneumonia of the base of the right lung. Convalescence was interrupted by a severe relapse six weeks later which was followed by two years of invalidism.

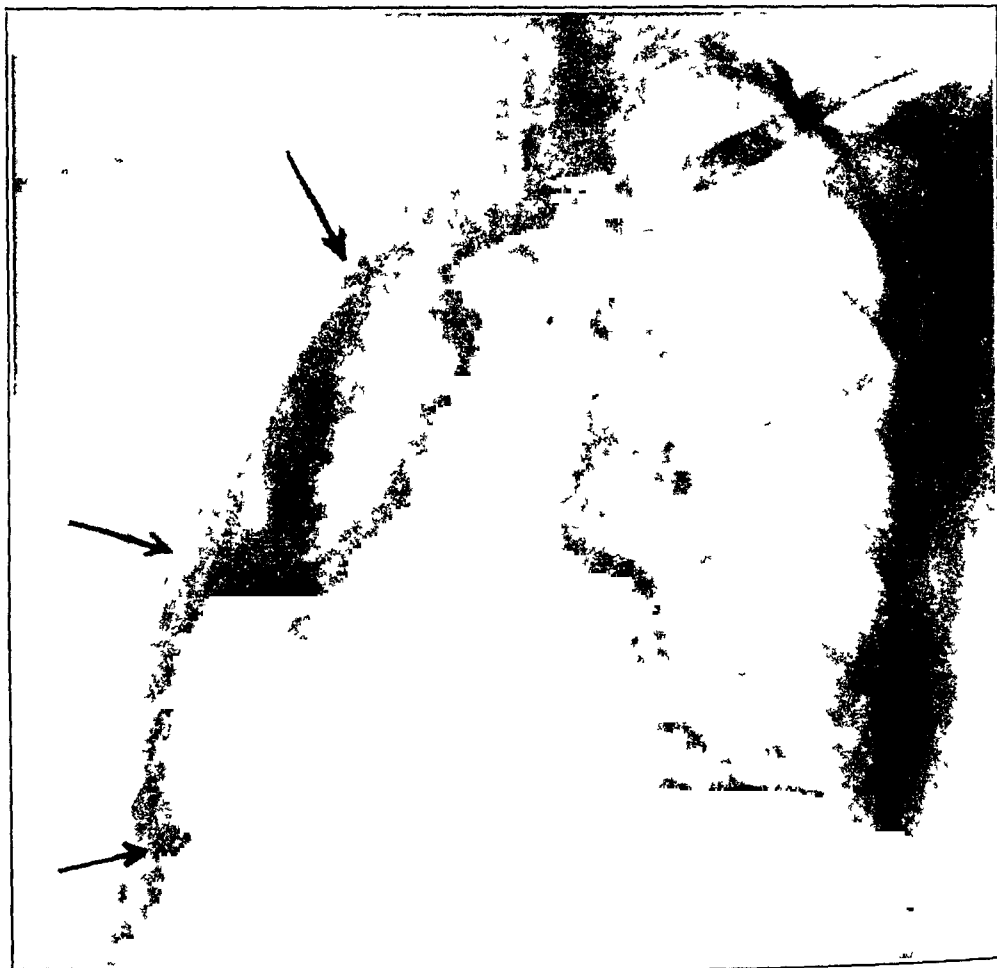


Fig 10 (Case 9)—The left pleura shows a massive cement-like formation in the form of a large sheet of calcareous degeneration, marking the seat of a severe empyema fourteen years ago.

in the army hospital. During this time, the army surgeons used frequent cupping of the right lung to promote resolution. It was four years before the patient was able to work. In all probability, the present extensive calcification at the base of the right lung is the terminal result of pneumonia followed by empyema about fifty-nine years ago.

CASE 6—Twelve years ago, Mr H E S, aged 32, was accidentally shot in the right superclavicular region with a 32 caliber bullet, which traveled downward, penetrating the right diaphragm and lodging in the abdomen. The patient was in bed for twenty-six weeks with cough and symptoms of lung

This patient had had severe pneumonia followed by empyema fourteen years before. The patient in Case 10 was suffering from a definite myocardial degeneration, the extensive calcified patch (Fig 11) involving most of the right pleura was, in all probability, the result of a pneumonia followed by empyema forty-three years before.

CASE 11—Figure 12 represents a calcareous plaque in the left pleura of a man, 75 years of age, with no definite history of pneumonia or empyema,

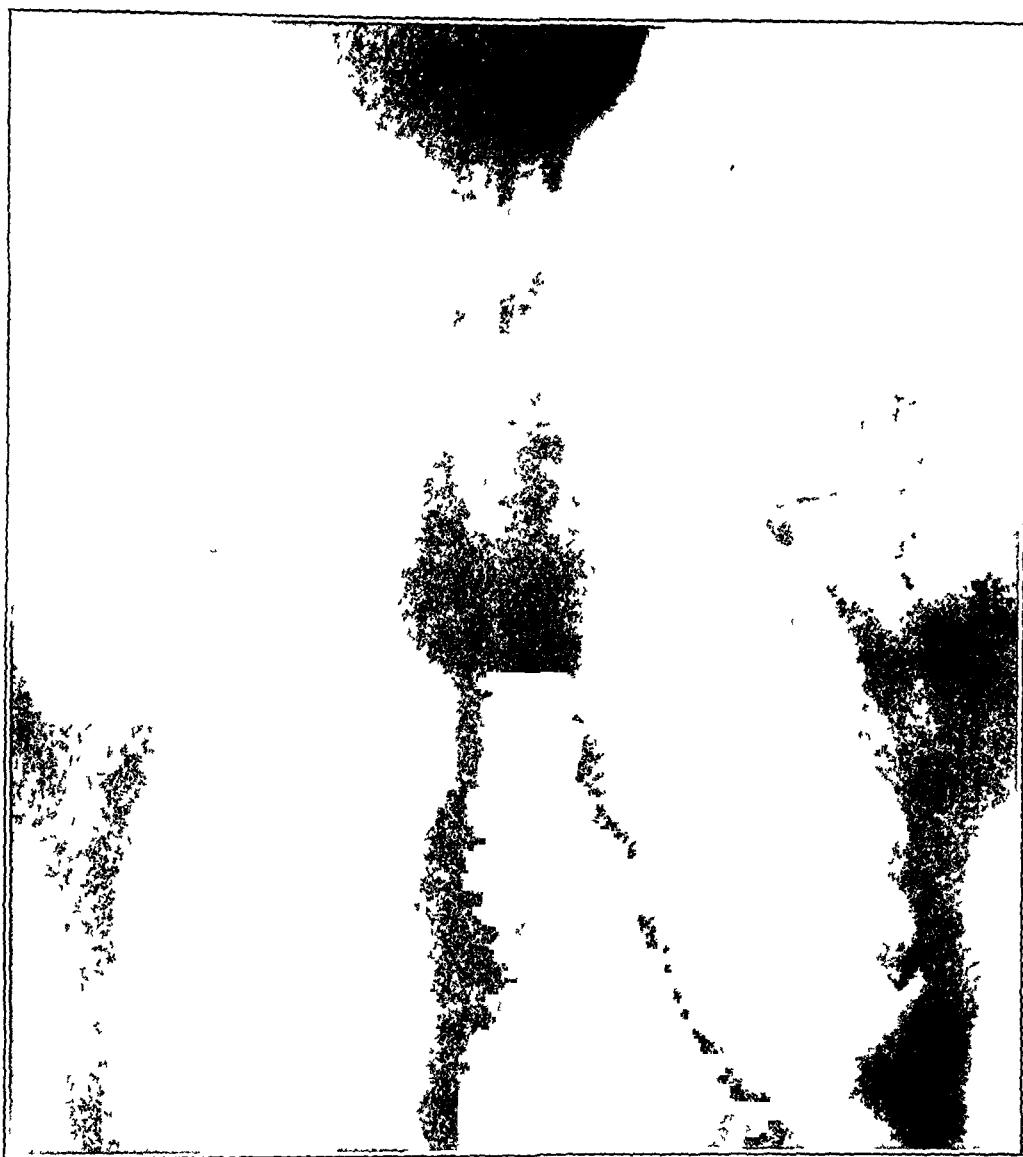


Fig 13 (Case 12) —The extensive calcification seen in the cervical glands in such uniform arrangement is unusual. The patient had what is reasonable to consider a chronic cervical adenitis (tuberculous) in early adult life. A substernal goiter is apparent.

except that at 20 years of age a severe attack of malaria (?) kept the patient in bed for three weeks. This isolated patch of pleural calcification is rather frequently found since the advent of the roentgen ray.

CASE 12—The case of Mrs. Mc is most interesting in that the history reveals distinct evidence of a definite cervical adenitis in early adult life when the glands would become enlarged and tender for weeks at a time, and this



For a number of years following this illness she was not considered strong, but she was free from any respiratory symptoms until about four years ago, when an unproductive cough developed, which in the light of the present examination could be attributed to the circulatory deficiency in the form of an aortic aneurysm (Fig 9)

Physical examination of the chest revealed extensive retraction of the right side with definite decreased resonance over the lower two thirds of the pulmonary area. Coarse râles and rhonchi were heard below the corresponding clavicle to the fourth rib



Fig 12 (Case 11) —An isolated calcareous plaque in the left pleura of a man 75 years old. The history of severe malaria at the age of 20 was the only suggestive evidence of pneumonia or empyema

Stercoroentgenograms of the chest (Fig 9) showed that the entire mediastinum was pulled to the right. There was a manifest aortic aneurysm, and the right lung was encased in a hard shell-like substance characteristic of an extensive deposit of lime salts at the seat of the pleuritis forty years before. The blood Wassermann test was negative. No acid-fast bacilli were found in the sputum.

CASES 9 and 10 —These patients had practically the same history as in the preceding case in that the patients had not suffered from any recent chronic respiratory ailment, but a definite empyema apparently existed years prior to the present investigation. In Case 9 there was massive cementing of the entire left pleura (Fig 10) in the form of a large sheet of calcareous degeneration

Stereoroentgenograms of the chest (Fig 14) showed an extensive substernal goiter, running down to the aortic arch, more enlarged on the right than on the left, and in this enlargement there was a large calcareous mass as big as a hickory nut, in the substance of the substernal goiter, opposite and below the inner end of the right clavicle. There was a smaller calcareous deposit, about half the size of the one on the left, in the right thyroid area, but this was above the suprasternal notch. The trachea was pushed toward the left. The heart was normal in size, but the aortic arch had a plaque of calcareous deposit, showing an atheromatous condition. The descending aorta

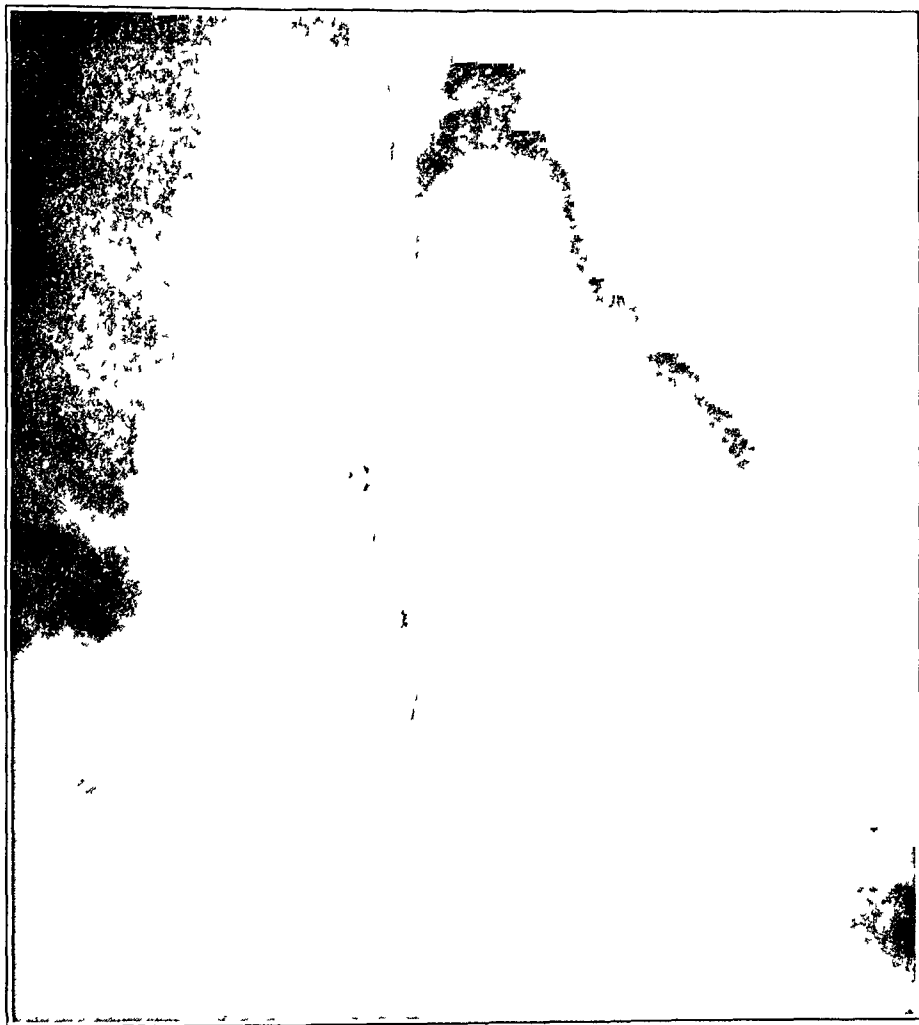


Fig 15 (Case 14) —Extensive calcification of the pericardium in a woman, associated with cirrhosis of the liver and ascites. (Reported by Dr J T Case J A M A 80 236 [Jan 27] 1923)

was distinctly widened in the form of a fusiform dilatation. The unproductive cough may be due to pressure of the calcified mass in the substernal goiter.

CASE 14<sup>50</sup>—Mrs Z R was apparently in good health until two years ago, when she slowly developed circulatory disturbances and later abdominal ascites.

The roentgen-ray chest plates (Fig 15) revealed a peculiar condition of the heart. In the left border, there was a semilunar calcified ring which appeared to be the result of some old pericarditis or diaphragmatic pleurisy. This cal-

<sup>50</sup> Case, J T. Pericarditis Calculosa. Report of a New Case Discovered Roentgenologically, J A M A 80 236 (Jan 27) 1923.

condition was always associated with a definite fatigue and ill health. The patient's mother died of pulmonary tuberculosis, two brothers died in their twenties of the same disease. The patient, who is now 50 years of age, had never been strong. She had always been underweight and nervous, she had acute nephritis after her second pregnancy, for a few years after this a cough persisted which was always considered bronchitis. The present symptoms and indisposition may be reasonably attributed to hypertension. The Wassermann test was negative. There were no respiratory symptoms. Stereoroentgenograms of the chest and cervical region (Fig 13) plainly showed an extensive calcification of the complete chain of cervical glands, the anterior and posterior

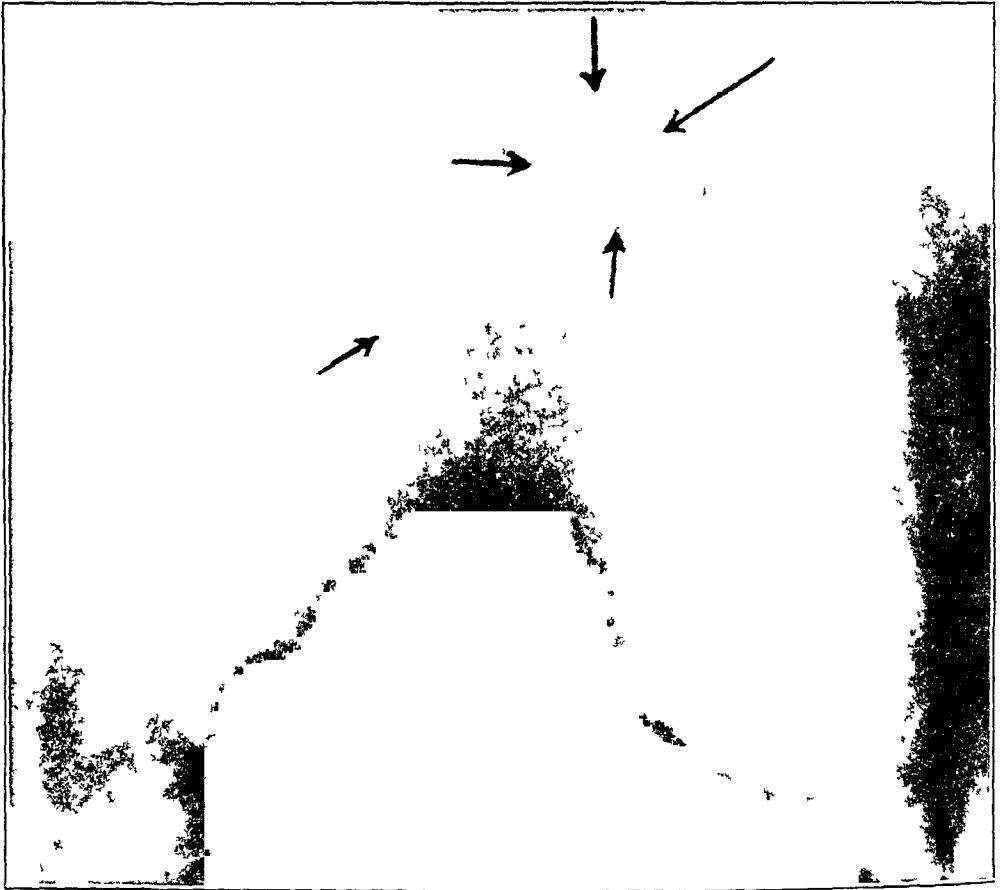


Fig 14 (Case 13) —A definite substernal goiter in this case shows a deposit of lime salts in the right side. It is unusual in that the calcification is entirely confined to the substernal portion of the goiter.

divisions were easily recognized. The history and roentgen-ray evidence mark this as a rather definite case of an obsolete tuberculous cervical adenitis followed by calcification.

CASE 13—Mrs S K, aged 52, gave a history of bronchopneumonia fourteen years before. She had never been strong and had had hemoptysis at the age of 20, seventeen years ago she had had a severe attack of coughing and spat blood, she had had influenza three years ago, and a persistent cough had been the sequence.

Physical examination of the chest showed an enlarged thyroid, particularly on the right, extending downward to the suprasternal notch. There was definite pulsation over this enlargement.

# OBSERVATIONS ON SALT IN VASCULAR HYPERTENSION \*

JAMES P O'HARE, M D  
AND  
WILLIAM G WALKER, M D  
BOSTON

Any therapeutic measure claiming efficacy in a given disease or condition should fulfil at least this primary condition It should be proved beyond a reasonable doubt that this measure, and this alone, produced the given result As a corollary to the main proposition, it may be fairly demanded that any maneuver claiming to be more effective than another should show that the former measure is definitely and measurably superior to the latter

In 1920, Allen<sup>1</sup> published a paper in which he asserted that a greater restriction in salt intake in cases of hypertension would produce a much greater reduction in pressure, a greater relief in symptoms, a speedier clearing up of retinal hemorrhages, etc, without other restriction in diet, exercise, etc, than other methods of treatment He advocated limiting the intake of salt to 0.5 gm a day instead of the usual 2 gm His claim, if true, would have been a welcome advance in our therapy of a troublesome and apparently increasing disease

This seemed, however, rather hard to believe for several reasons In the first place, there is no good foundation for the restriction of salt in cases of hypertension with the exception of those associated with nephritic retention The only reason given for the almost universal restriction of salt in treating hypertension is based on the assumed decreased viscosity of the blood resulting therefrom But this is mere assumption and not proved or accepted Perhaps the close relation between chronic nephritis (with salt retention) and vascular hypertension is responsible for the salt reduction treatment Perhaps, it is pure empiricism or a clever method to prevent overeating by rendering the food less palatable

In the second place, it was hard to believe that a reduction in salt intake from 2 gm to 0.5 gm would prove so much more effective than the restriction from 10 gm to 2 gm, as had been tried frequently

Then, too, it seemed hard to understand the comparatively low pressure of subacute nephritis and chronic nephritis with edema Only

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\* From the Medical Clinic of the Peter Bent Brigham Hospital

\* This paper was read by title at the meeting of the American Society for Clinical Investigation in Washington, May, 1922

\* This paper is the second one of a series of studies in metabolism from the Harvard Medical School and allied hospitals The expenses of this investigation have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases

1 Allen, F M Arterial Hypertension, J A M A 74 652 (March 6) 1920

cification was in the pericardium. A left oblique pair of stereoroentgenograms showed that this circular patch was situated in front of the anterior cardiac wall. It gave the appearance of an extensive irregular calcified patch about 8 cm in every diameter, ovoid and flat in appearance.

The physical examination showed decreased resonance over the back of both lungs in the lower half, accompanied by medium sized râles suggesting a chronic venous congestion.

CASE 15—Mrs J, aged 51, complained of an intermittent diarrhea of many years' duration. A year ago an exploratory laparotomy failed to reveal any cause of the dysentery. A carefully taken history did not elicit the existence

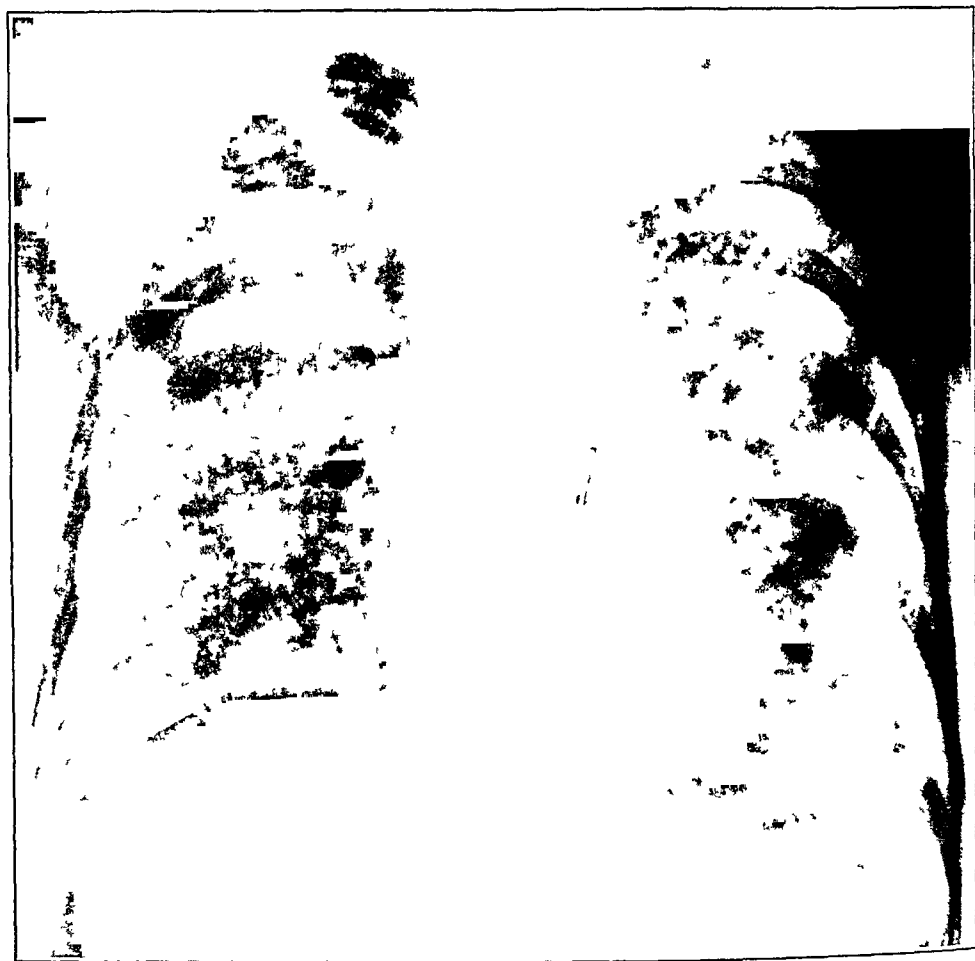


Fig 16 (Case 15)—An apparent calcareous metastasis in a woman of 51 years. There was no history of respiratory disease or chronic osseous affections. Seven years later stereoroentgenograms gave the same appearance. The Wassermann test was negative.

of any present or past chronic respiratory disorder. Physical examination of the chest showed little or no abnormality.

Stereoroentgenograms of the chest (Fig 16) give a dramatic picture in the form of a complete and evenly distributed peppering of the whole pulmonary field with small shot-like, clean-cut deposits characteristic of calcification metastasis. No history of disease of the osseous tissue was obtained. Seven years later the patient returned and the stereoroentgenograms of the chest showed the same appearance. The Wassermann test was negative on both occasions.

## BLOOD PRESSURE AND WHOLE BLOOD CHLORIDS IN THIRTY-THREE PATIENTS

Chart 1 demonstrates some significant facts. Although none of the blood chlorids is above normal, twenty of the thirty-seven pressures are above normal. Eight patients had systolic pressures of over 200 and three had diastolic pressures of 120 or over. More significant even

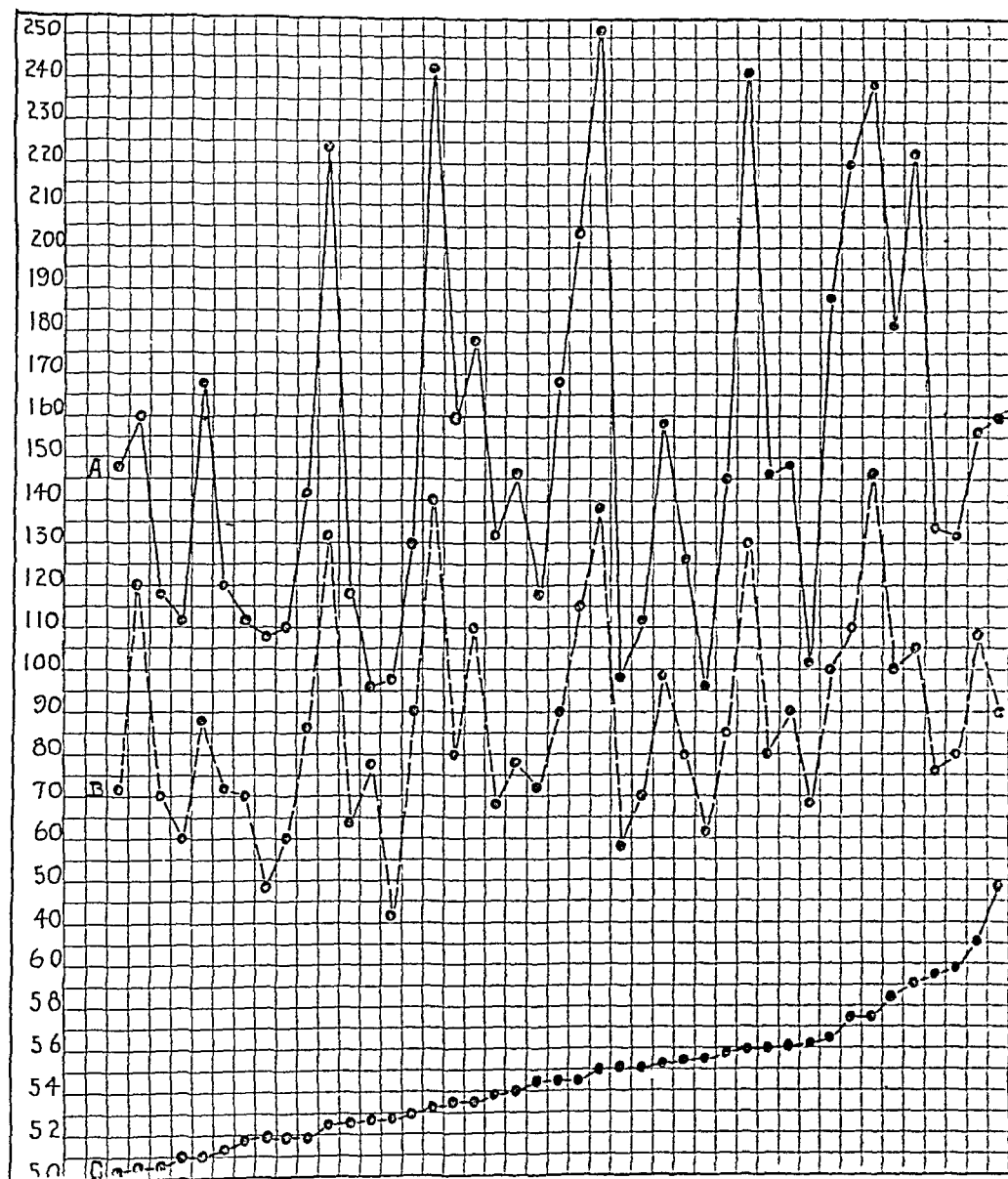


Chart 2—Forty-three determinations on twenty-four patients. Twenty-three had hypertension. Arrangement is the same as in Chart 1. *A* represents systolic blood pressure, *B*, diastolic blood pressure, *C*, whole blood chlorid in grams per liter. The whole blood chlorids are all above normal.

is the contrast between the curve representing the blood chlorids and those of the pressures. The pressures are represented by absolutely irregular types of curves without any relation to the blood chlorid curve,

rarely is hypertension seen in these conditions, and yet they show the greatest retention of salt

Furthermore, if the salt is such a determining factor, we should expect to find the blood chlorid increased in our hypertension cases and a definite relation existing between the level of this substance and that of the blood pressure Charts 1, 2 and 3 throw some light on this subject

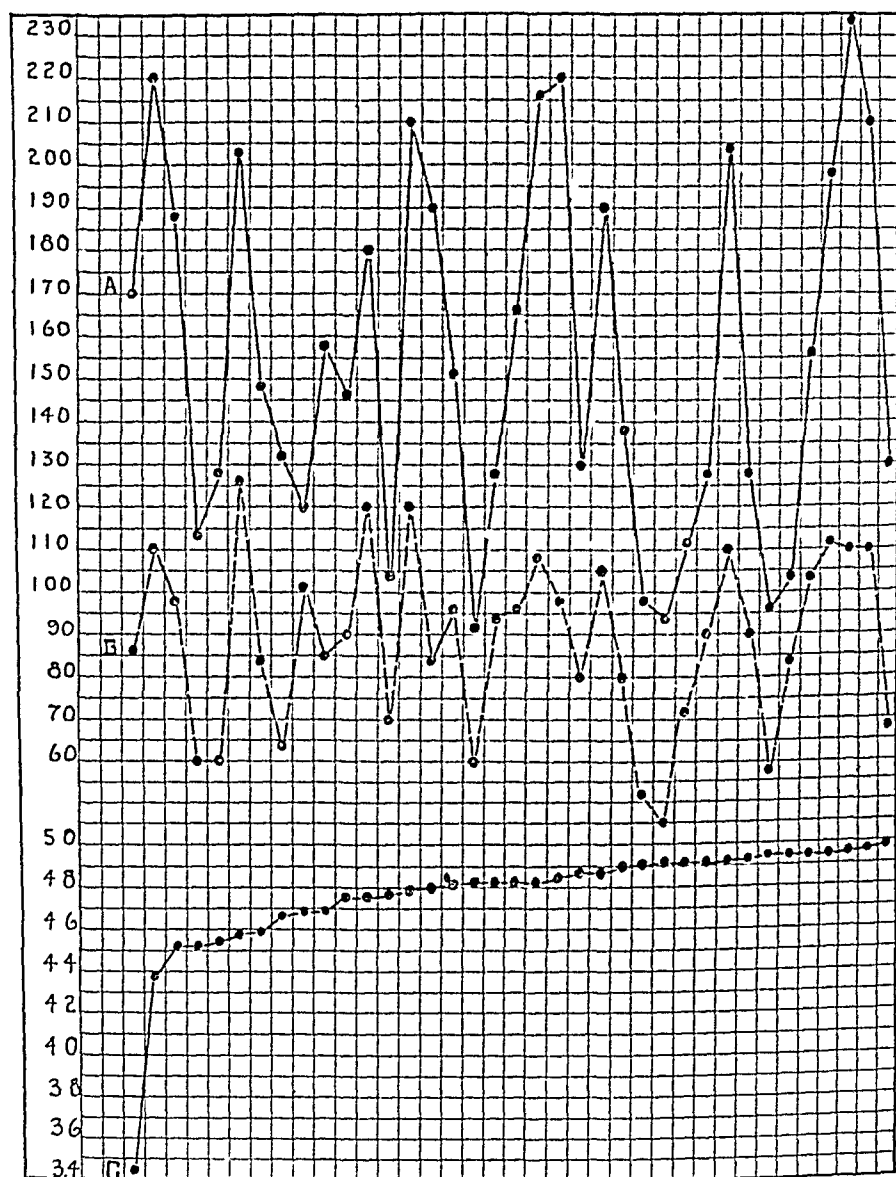


Chart 1—Thirty-seven determinations of blood pressure and whole blood chlorid on thirty-three patients. Pressure and chlorid determined on the same day. Twenty of the thirty-seven had hypertension. The arrangement is according to an ascending value of the blood chlorid. All of these except the lowest are within the accepted limits of normal. The commonly accepted limits for normal according to Myers, McLean and Berglund are 4 to 5 gm per liter of whole blood and 5.62-6.25 gm per liter of plasma. Berglund feels that even 5.2 gm per liter of whole blood is normal. In the chart *A* represents systolic blood pressure, *B* diastolic blood pressure, *C* whole blood chlorid in grams per liter.

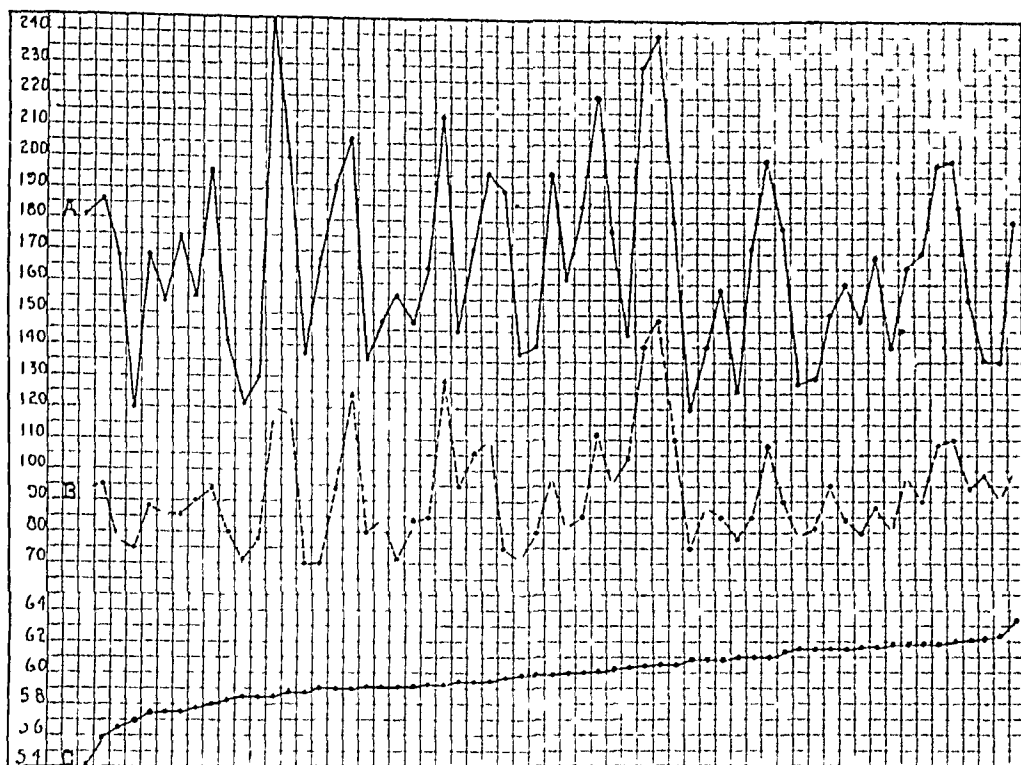


Chart 3—Sixty-one determinations of blood pressure and plasma chlorids on thirteen patients. All cases but the first have been diagnosed as vascular hypertension, although seventeen at the time showed a normal pressure. The plasma chlorids are all within the accepted limits of normal, except the first two which are low, and the last which is high. The arrangement is the same as in Chart 1. *A* represents systolic blood pressure, *B*, diastolic blood pressure, *C*, plasma chlorid in grams per liter.

TABLE 1—Cases in Which Plasma Chlorids and Blood Pressures Have Been Repeated

Medical No	Plasma Chlorid	Blood Pressure		Medical No	Plasma Chlorid	Blood Pressure	
		Systolic	Diastolic			Systolic	Diastolic
12,459	5.83	112	80	15,402	5.91	156	72
	5.85	122	72		5.91	118	81
	5.86	130	78		5.93	165	85
	5.89	138	70		5.96	196	110
	5.99	138	72		5.99	110	80
	6.09	170	75		6.00	162	82
	6.18	140	80		6.10	172	85
	6.11	178	90		6.18	165	98
	6.15	150	95		6.20	200	110
	6.18	170	90				
17,285	5.41	182	91	15,811	5.95	145	99
	5.58	166	95		6.04	141	101
	5.65	168	78		6.06	180	110
	5.75	168	88		6.15	128	78
	5.76	171	86		6.23	176	98
	5.76	151	86		6.21	176	90
	5.78	156	90	17,477	5.86	244	120
	5.80	196	91		5.88	200	118
	5.91	136	80		5.90	206	124
	5.99	196	98		5.93	214	118
	6.01	220	112		6.05	270	140
	6.09	140	88		6.06	210	148
	6.09	158	85	16,202	6.03	177	95
	6.10	126	78		6.16	168	88
	6.15	130	82		6.16	148	80
	6.15	100	81		6.18	198	108
					6.21	155	91
					6.31	180	100



which steadily climbs. High systolic and diastolic pressures may be found corresponding to low values of chlorid and normal or low pressures associated with the higher chlorids in this chart. The chart demonstrates that hypertension is compatible with normal or low blood chlorid, and that there is no relation between the levels of the chlorid and the pressures.

Chart 2 is similar to Chart 1. However, all of the blood chlorids in this chart are above normal. Despite this fact, twenty of the forty-three pressures are normal or low. The contrast between the steadily rising curve of the blood chlorids and the absolutely irregular, jagged curves of the pressures is as marked as in Chart 1. It may be pointed out that there are many higher pressures, both systolic and diastolic, in this group than in the one preceding. On the other hand, there are many lower. In our first chart, there are only two systolic pressures as low as 120, whereas in the second chart there are fourteen. Chart 2 indicates that a normal or low blood pressure is compatible with a high blood salt content, and that there is no relation between the levels of chlorid and pressure.

#### BLOOD PRESSURE AND BLOOD PLASMA CHLORIDS IN VASCULAR HYPERTENSION

Chart 3 illustrates the facts brought out in the two previous ones. The single high plasma chlorid in so many patients with hypertension is especially noteworthy.

These three charts demonstrate that in different persons (1) hypertension is compatible with normal blood chlorid, (2) normal tension is compatible with high blood chlorid, (3) there is no relation between the height of the blood pressure and that of the blood chlorid.

Such conclusions apply also to the same determinations in the same patient.

The figures in Table 1 speak for themselves and indicate that in the same patient, as well as in different patients, there is absolutely no relation between the level of the plasma chlorid and the blood pressure. In the fourth, fifth and sixth patients in this group, it is interesting to note the pressures corresponding to the lowest and highest chlorids. They are almost alike.

Another doubt is cast on the relation between the blood pressure and the chlorid metabolism. It seems difficult to imagine that changes in the salt metabolism of the body could take place rapidly enough to bring about the sudden and often marked changes that take place in the blood pressure from second to second and from minute to minute.<sup>2</sup>

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<sup>2</sup> O'Hare J. P. Vascular Reactions in Vascular Hypertension. *Am J M Sc* 159 369, 1920. Common Sense in the Interpretation of Hypertension, *Clin North America*, 5 1349 1922.

It is hard to believe that the salt has anything to do with such a marked change in pressure in such a short period of time as is illustrated in Chart 9. Note particularly the change of over 100 mm systolic and 55 mm diastolic pressure in twenty-four hours on March 1. Such a tremendous change, one would feel, must assume an equivalent change in chlorid metabolism. The urine and plasma chlorids indicate no such change. Furthermore, we know that any such marked change would be extremely dangerous to life. It is certain in this case that nervous influences were responsible, and it is hard to believe that these act on the vessels through sudden changes in salt metabolism.

In spite of the doubts that crept into our mind, it seemed desirable to check up the very low salt regimen to discover whether it fulfilled the requirements mentioned in the introduction of this paper. At first thought this might seem a simple, straightforward piece of work. Our original plan was to place patients with hypertension, on alternate weeks, on a 0.5 gm and 4 gm salt regimen. Many practical difficulties were soon encountered. The chief of these was our inability to get, in one week, dechloridization sufficient to bring the case within the accepted limits of an excretion of salt of 0.5 gm or less a day. This necessitated, as a rule, the use of long periods of low salt intake and shorter control periods. Rarely could our patients stay in the hospital long enough to allow a period of higher salt intake comparable in length to the low salt period. This time variable should be borne in mind in the interpretation of the results.

Since the reduction in pressure was the only measurable criterion, we felt that we should use cases of pure hypertension and exclude those complicated by nephritis. Eighteen cases of vascular hypertension, therefore, were selected. Our aim was to have these patients under as constant conditions as possible during the experiment. They were, therefore, all kept at rest in bed during the entire period of observation. All were given a fixed diet containing 60 gm of protein, 2,000 calories, and 1,800 c c of fluid. The only (controllable) variation was in the salt intake, which was alternately 0.5 gm and 4 gm. (The latter amount was selected instead of 2 gm to exaggerate any differences due to the low salt content.) Practically the only variable over which we had no control was nervous influences. These played, however, an important part.

Blood pressure readings were taken at the same time each day. The chlorid in the urine was quantitated daily to control the intake. The plasma chlorid was determined, as a rule, once a week.

The only good way to view the results of this study is to see the charts. For obvious reasons, only a few can be included here. A table such as Table 2 is the most easily available way to present the data in print. Necessarily, it is somewhat imperfect.

TABLE 2—Effect of Alternate Low Salt and Higher Salt Intake

Case	Period	Duration in Days	Systolic and Diastolic Pressures at Onset	Highest Systolic Pressure	Lowest Systolic Pressure	Variation in Systolic Pressure	Average Systolic Pressure	Difference in Average Systolic Pressure	Highest Diastolic Pressure	Lowest Diastolic Pressure	Variation in Diastolic Pressure	Average Diastolic Pressure	Difference in Average Diastolic Pressure
1	05	16	190/100	195	140	55	168	+11	110	80	30	92	+3
	40	18	145/85	185	135	50	154		100	75	25	89	
2	40	9	124/64	130	124	6	127	+12	70	64	6	67	+10
	05	15	131/66	150	122	28	139		88	64	24	77	
3	05	8	180/110	180	120	60	137	+9	110	80	30	88	+2
	40	7	105/80	110	105	5	120		90	80	10	86	
4	05	15	204/110	208	173	35	193	+3	106	92	14	99	0
	10	15	182/94	220	174	46	190		112	90	22	99	
	06	64	196/98	196	176	60	167	(25)	105	78	28	84	15
5	05	13	168/60	172	156	16	165	0	70	58	12	62	+2
	40	8	158/54	174	156	18	165		70	54	16	60	
	05	11	162/60	170	152	18	159	(6)	70	56	14	63	+3
6	40	10	150/78	150	134	16	141	1	83	64	19	73	+5
	05	12	138/74	152	128	24	110		84	68	16	78	
7	40	6	230/140	266	230	36	247	1	148	130	18	142	10
	05	38	254/150	256	192	64	246		164	122	42	182	
8	05	16	178/94	200	140	60	162	4	98	74	24	88	+2
	40	15	162/82	180	156	24	166		98	80	18	86	
	05	15	168/88	182	148	34	164	(2)	102	72	30	89	+3
9	40	7	188/135	188	160	28	175	5	135	110	25	124	13
	05	25	153/110	200	150	50	170		132	104	28	111	
10	40	8	200/130	220	185	25	204	7	135	125	10	131	3
	05	18	220/140	220	170	50	197		140	105	35	129	
11	40	15	225/95	255	215	40	229	11	110	85	25	98	4
	05	31	225/100	243	140	103	218		120	70	50	94	
	40	18	215/85	210	200	40	218	(0)	110	85	25	90	+4
12	40	9	214/130	214	180	34	201	13	130	105	25	119	5
	05	20	198/110	202	160	42	188		120	94	26	114	
13	40	7	170/90	205	162	43	185	18	105	80	25	91	0
	05	40	178/90	195	145	50	167		105	80	25	91	
14	40	8	180/90	210	180	30	194	10	120	90	30	106	14
	05	38	185/95	260	135	125	175		140	75	65	92	
15	40	8	193/98	220	150	70	200	22	110	80	30	99	0
	05	14	212/100	215	150	65	178		110	90	20	99	
16	40	13	250/130	250	220	30	234	22	142	116	26	129	10
	05	11	228/114	232	194	38	212		138	108	30	119	
17	40	6	206/100	244	206	38	233	24	130	100	30	118	16
	05	22	224/122	224	190	34	209		112	90	22	102	
18	40	10	200/122	240	185	55	205	40	150	105	45	126	19
	05	35	198/118	220	132	88	165		140	90	50	107	
	100	6	148/90	184	145	39	161	(+4)	110	90	20	106	+1

Another fact brought out previously is that the pressures not infrequently fall materially (40 or more millimeters, systolic) without any special treatment except physical and mental rest. Note the decrease of 68 mm and 56 mm in systolic pressure and 48 mm and 20 mm in diastolic, in the first patient in Chart 5.

This patient was given no special treatment except rest in bed. The diet was "house diet," with no restrictions in salt. The second patient in this chart showed a drop of 35 mm systolic and 25 mm diastolic pressure, in spite of the fact that the patient was getting 4 gm of salt.

If the 0.5 gm salt regimen is effective, it seems to me that we should expect (1) a definite decrease in the variations, and (2) a material lowering of the pressure, about which there can be no question. With regard to the second point, we think it is fair to demand an average decrease in systolic pressure of 25 mm and, perhaps, somewhat less in the diastolic. Anything less is doubtful and can easily be accounted for by the physical rest or mental ease obtained.

Let us now return to Table 2. An analysis of the columns headed "Variation in Systolic" indicates that there were wider variations in both systolic and diastolic pressures during the 0.5 gm regimen. Seventeen times during the low salt regimen, the degree of fluctuation was greater. It was less only four times and the same once. As for the diastolic pressure, the figures are about the same: greater fluctuation during the low salt regimen fifteen times, less six times and the same once. These are brought out better in the charts than in this table. Certainly the low salt regimen does not prevent the wide swings in pressure so common in these patients.

Analysis of the columns headed "Difference in Average Systolic" and "Difference in Average Diastolic" shows that only Cases 4 and 18 can reasonably be assumed to show sufficient change in pressure during the 0.5 gm regimen to admit the possibility of the low salt ingestion being effective. While such is a possible interpretation, certain doubts are cast on the truth of such interpretation. In Case 4, it is only in the prolonged sixty-four day second period that the pressure fell so much. In the first low salt ingestion period, in which the duration was identical with the control period, there was actually a slight difference in favor of the latter. Furthermore, when this patient was allowed much larger amounts of salt, there was no evident relation between the pressure and the amount of salt excreted (see Chart VI). In Case 18, too, there is some doubt because on an intake of 10 gm of salt per day for six days, this patient had an average systolic pressure that was actually 4 mm less than during the low salt period. This table does not indicate that the 0.5 gm intake is of greater value than the 4 gm salt diet.

The arrangement of patients is in order of differences in the average systolic pressures. A plus sign indicates that the pressure was lower with the 4 gm than with the 0.5 gm intake. In the first column is indicated the salt period—either 0.5 gm or 4 gm. In the given case, the arrangement of the periods is chronologic. The second column indicates the duration of the periods in days. (It will be noted that the 0.5 gm period is often considerably longer than the control period. It has, therefore, the added advantage of longer rest in bed, etc.) In the next column is given the systolic and diastolic pressures at the onset of the experiment. The next two columns contain the highest and lowest systolic pressures and the following one the difference between these two. These three give us the range of fluctuation. The next column

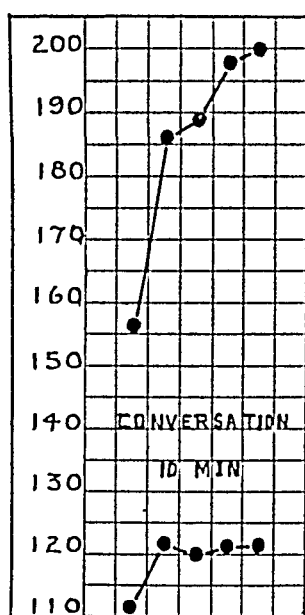


Chart 4—Effect of conversation. Pressures taken every two minutes.

gives us the average systolic pressure. The one following indicates the difference between the average systolic pressures in the periods. The remaining columns are the same for the diastolic pressure.

Before analyzing these figures in detail, let us see what previous experience with patients with hypertension has taught us. This will enable us to judge our results more correctly and to avoid the extremely common error of misinterpretation.

This experience has shown clearly that the pressure is extremely variable from minute to minute.<sup>2</sup> Systolic changes of 25 mm to 40 mm are not uncommon.

Chart 4 illustrates a striking effect of ordinary conversation in one of our nervous patients with hypertension. In her, the systolic pressure jumped 30 mm within two minutes of the beginning of a simple conversation. In ten minutes, this pressure had climbed from 156 to 200

Further evidence of the lack of relation between salt and hypertension is illustrated by four of our cases in which the patients took large amounts of salt, either at our suggestion or of their own free will. Case 18, Table 2, I have mentioned. This patient took 10 gm of salt a day for six days. The table shows that during this period the fluctuations in pressure were less and the average pressures somewhat lower than during the 0.5 gm salt regimen. Three more patients were

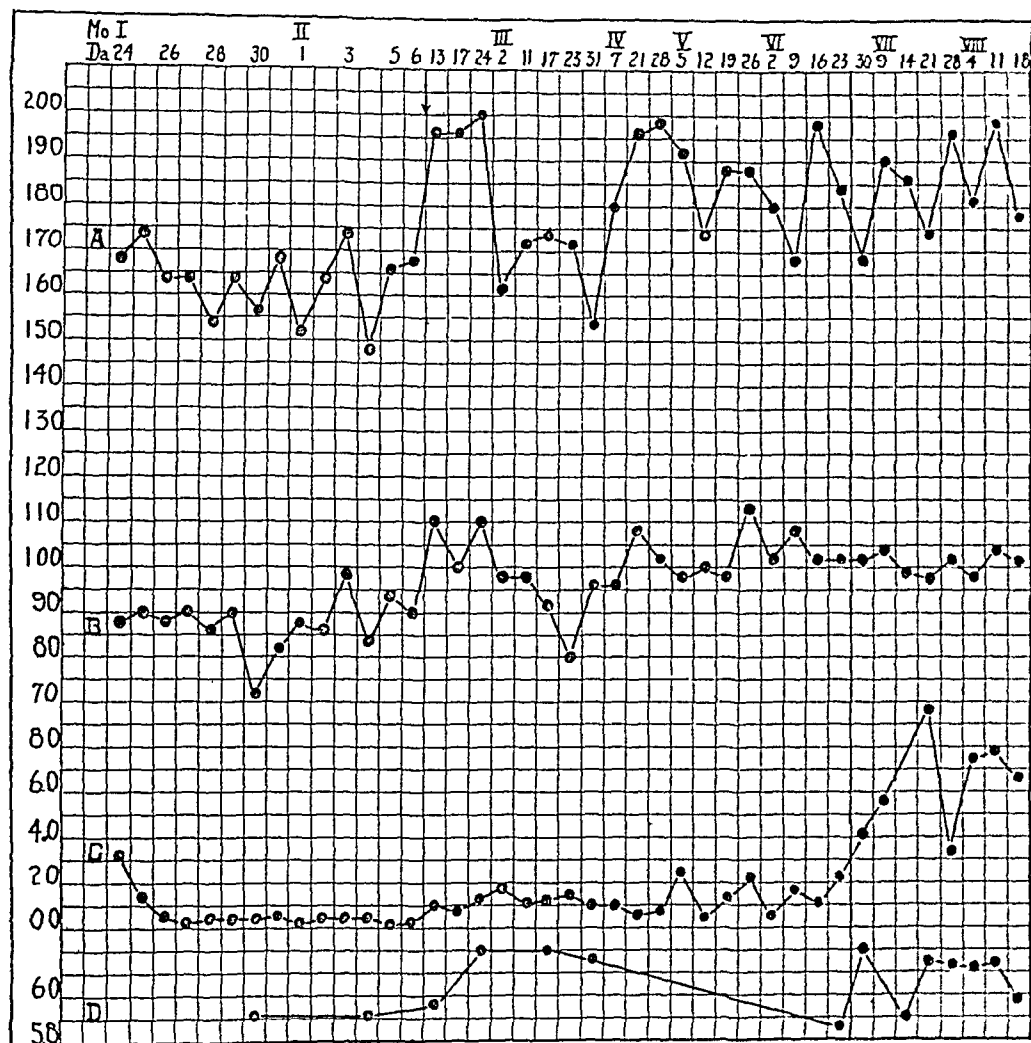


Chart 7—Excerpt from record of Case 8. Patient discharged from hospital on February 7. *A* represents systolic blood pressure, *B*, diastolic blood pressure, *C*, twenty-four hour urine chlorid in grams, *D*, plasma chlorid in grams per liter.

followed after their discharge from the hospital, and the effect of increased salt ingested was noted.

It will be noted in Chart 6 that up to June 18 this patient was taking only enough salt to excrete less than 0.5 gm. After that date she took a greater and variable amount as indicated by the urine chlorid. As one looks at the chart the first impression is that with the increased salt intake, the pressure, especially the systolic, rose. However, a little

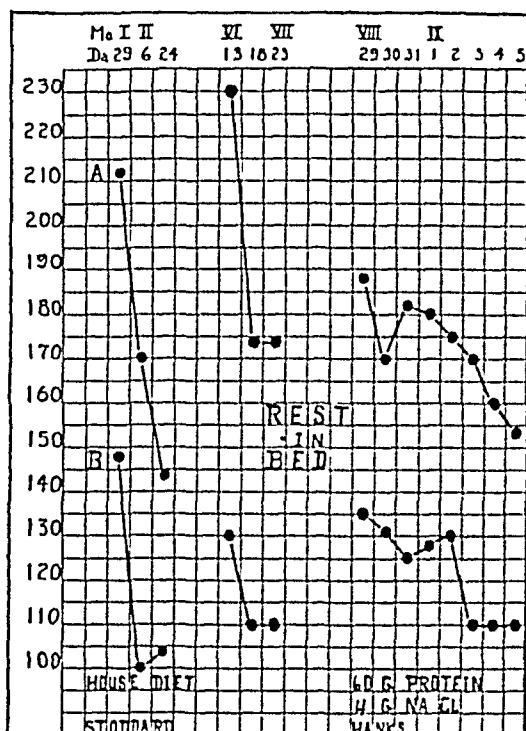


Chart 5—Effect of rest in bed At the top of the chart is indicated the month and just below it the day of the month .A represents systolic blood pressure, B, diastolic blood pressure

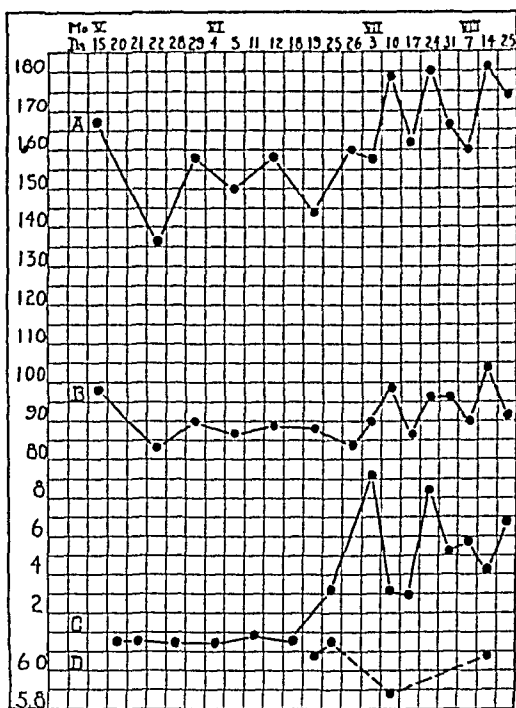


Chart 6—Excerpt from the record of Case 4, illustrating the result of increased salt intake A represents systolic blood pressure, B, diastolic blood pressure, C, twenty-four hour urine chlorid in grams, D, plasma chlorid in grams per liter

level? A point brought out in the previous chart is illustrated again here. On July 21, this patient's salt output was almost 10 gm, and yet the systolic pressure was much lower than on several other days when the excretion was between 0.5 gm and 1 gm. On July 28, a

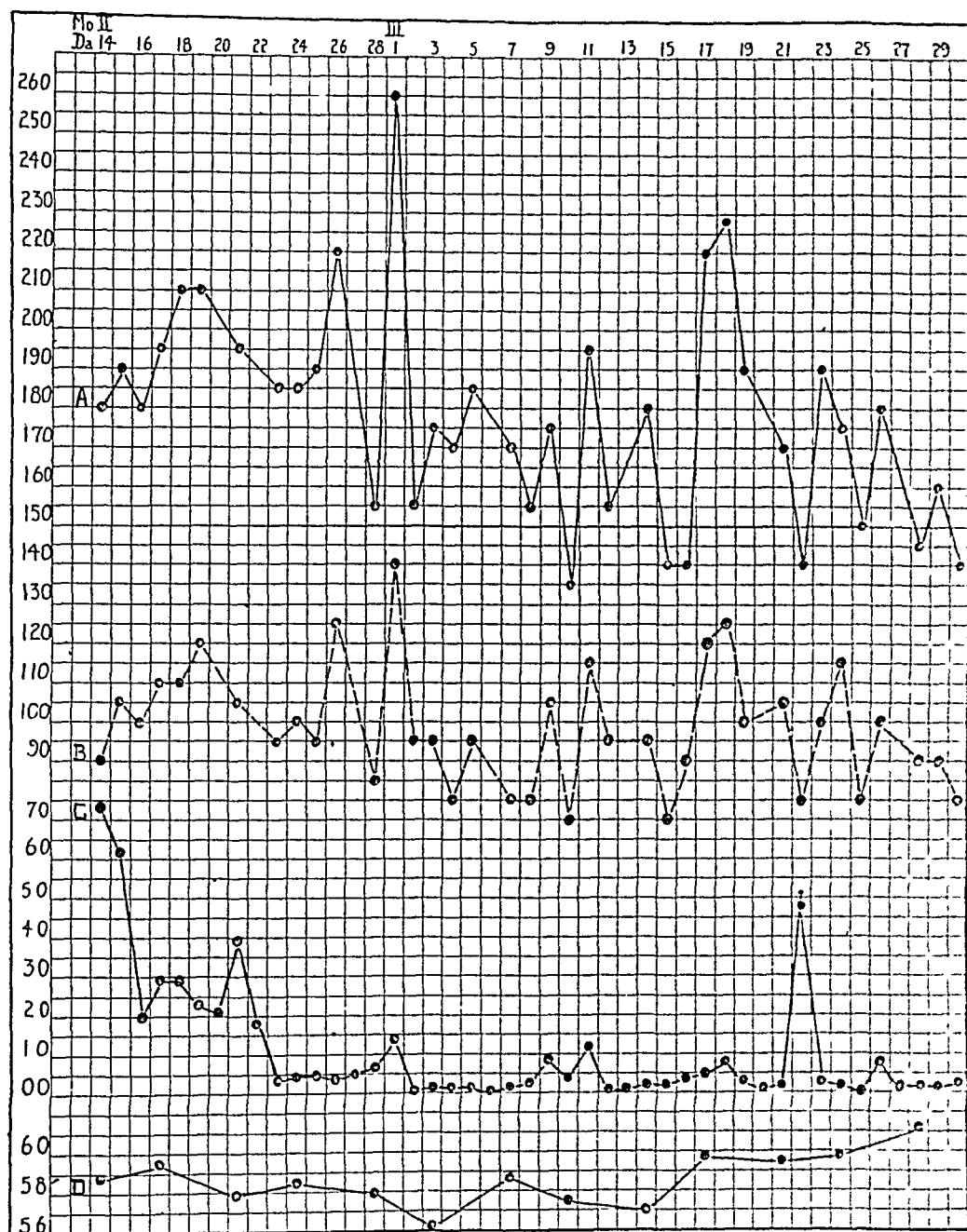


Chart 9 (Case 14) —This illustrates the effect of nervous influences. *A* represents systolic blood pressure, *B*, diastolic blood pressure. *C*, twenty-four hour urine chlorid in grams, *D*, plasma chlorid in grams per liter.

fall in salt to almost 3 gm was accompanied by a rise of 22 mm systolic pressure. The diastolic pressure was fairly constant.

This chart is almost similar to the previous two except that it is somewhat more striking. There are four things that are especially



closer inspection of this period will show that while this is true, there is really no relation between the salt and the blood pressure. For, on July 3, the output of salt registered over 9 gm, and yet the blood pressure was the lowest in that period and just about what it had been in the 0.5 gm period. On July 10, with a fall in the urine salt to 3 gm and a fall also in the plasma chlorid, the systolic pressure rose 22 mm and the diastolic 9 mm. Such observations make me feel certain that the general rise in pressure was due to factors other than salt.

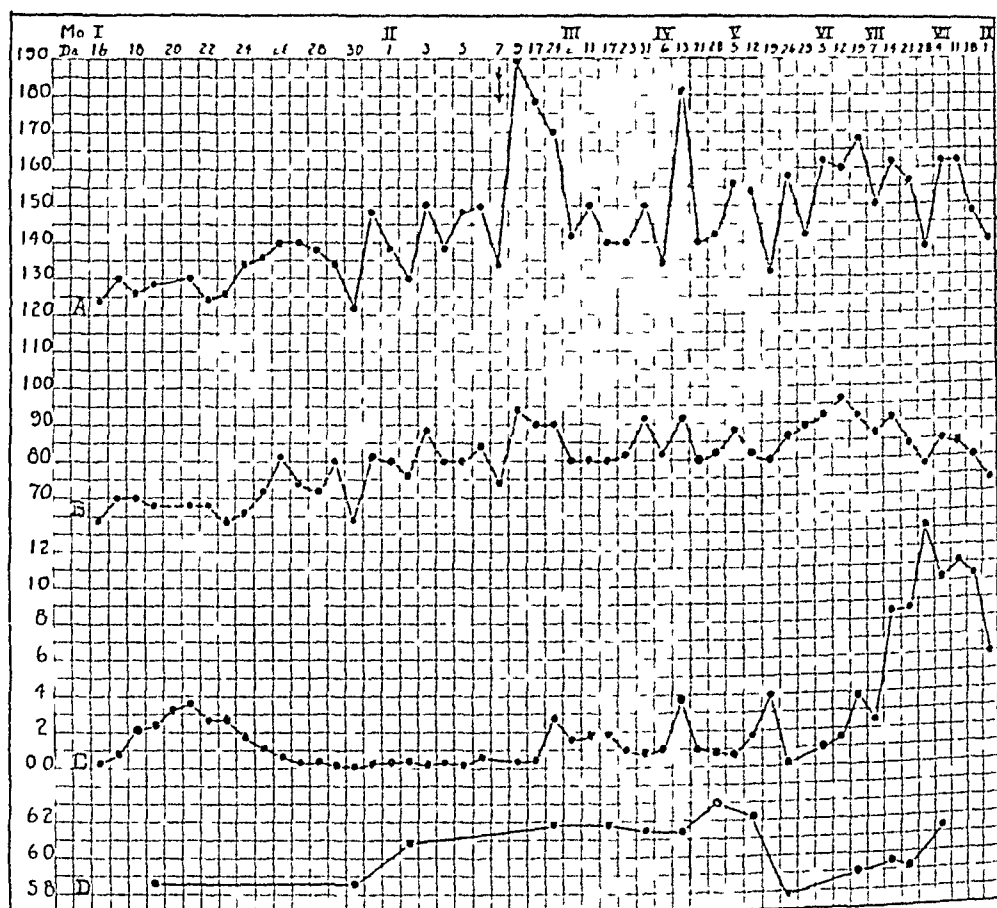


Chart 8—Excerpt from record of Case 2. Patient discharged from the hospital on February 7. *A* represents systolic blood pressure, *B*, diastolic blood pressure, *C*, twenty-four hour urine chlorid in grams, *D*, plasma chlorid in grams per liter.

Case 8 is similar in many respects to the previous one. One may note in the chart that after the patient's discharge from the hospital and with her return to home conditions, there was a sharp rise in both systolic and diastolic pressure. There is no comparable change in salt excretion, which shows only a slight rise. It is not possible to believe that the latter had anything to do with the rise in pressure. If so, why should the latter continue to stay at approximately the same level when the salt excretion rose subsequently to seven or eight times its former

pressure following the decrease to an 0.5 gm intake. One may point, by way of objection, to the rise in plasma chlorid with this rise in pressure. The former, however, is still within normal limits. Furthermore, we have previously demonstrated the lack of relation between the plasma chlorid and blood pressure. Lastly, this does not at all influence our main contention that the 0.5 gm salt intake does not materially decrease the pressure.

#### CONCLUSION

The experiences detailed above, with the extremely low salt intake advocated for the treatment of hypertension, do not indicate any special advantage over the older less rigid restriction. The former regimen has certainly not fulfilled in our patients the conditions mentioned in the introduction. This very low salt diet is, furthermore, difficult to carry out at home, is monotonous and expensive. This paper also suggests that salt plays little part in vascular hypertension.

worthy of note. The first is the gradual rise in pressure, in spite of a low salt excretion, before the patient was sent home. The second is the sharp rise of 58 mm systolic and 20 mm diastolic pressure two days after leaving the hospital. At this time, the salt excretion was 0.5 gm. Such a rise was undoubtedly the result of conditions at home. The excretion on July 28 of over 13 gm of salt with a pressure that fell to normal is especially noteworthy. Last but not least is the tendency for the systolic and especially the diastolic pressure to fall slightly during the very high salt feeding.

It is hard to believe from these experiences with high salt intake that the salt has much to do with the level of the blood pressure.

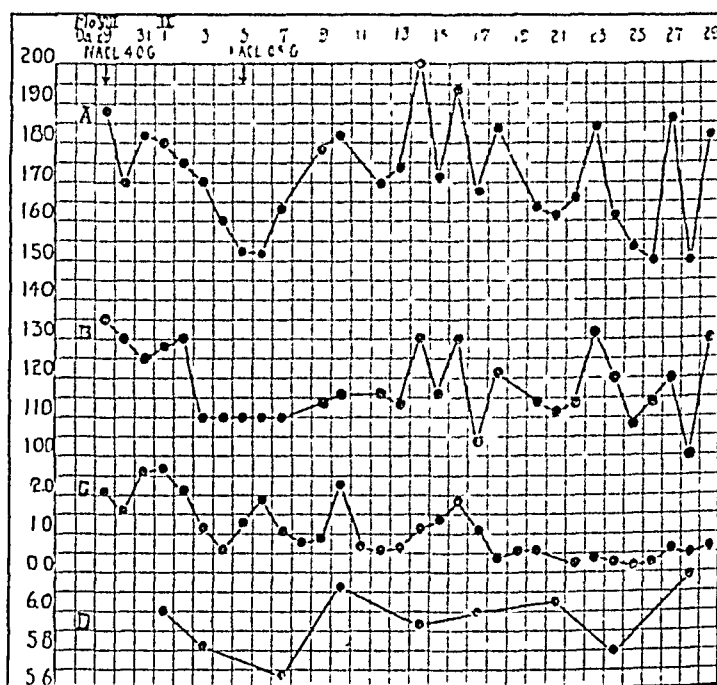


Chart 10 (Case 9)—The patient was on a 4 gm salt intake diet up to September 5. From that date he was taking only 0.5 gm. A represents systolic blood pressure, B, diastolic blood pressure, C, twenty-four hour urine chlorid in grams, D, plasma chlorid in grams per liter.

Two charts are appended which illustrate various obvious difficulties in accepting the idea that low salt intake is effective in hypertension. Chart 9 demonstrates the extreme variability in pressures that, to say the least, is not prevented by the very low salt diet. Note particularly the sharp changes in pressure on March 1 and 17, with no corresponding changes in salt excretion. An increase of 105 mm and 80 mm systolic and 55 mm and 30 mm diastolic pressure in twenty-four hours is difficult to attribute to the changes that took place in the salt at those times. In Chart 10, note particularly the primary fall in pressure during the 4 gm salt regimen and the paradoxical marked rise in

often following the ingestion of certain foods, and gastro-intestinal upset presenting a variety of symptoms), the bladder symptoms (frequent painful urination), and headache, nervousness, asthemia, hypotension and the like. The foregoing symptoms always suggest the possibility of allergy, especially when they occur in the absence of other apparent adequate cause for an illness, and when the family history is positive.

#### PHYSICAL EXAMINATION

The more important signs of allergy which can be found on physical examination are the ocular, the nasal, the bronchial and the cutaneous. The cutaneous symptoms can often be brought out by scratching the skin. This occasionally gives rise to the immediate appearance of typical wheals. Examination is also important in excluding sources other than allergy for a given complaint. For example, if, in a patient with a long history of frequent and painful urination, physical, cystoscopic, endoscopic and roentgen-ray examination, and uranalysis reveals nothing abnormal, bladder allergy must always be suspected, especially if the patient gives a history of hives, asthma or other characteristic symptoms of the condition, and if a history of such symptoms in the parents can be obtained.

#### OBSERVATIONS BY THE PATIENT

Practical observation by both physician and patient is important. It is often advisable, in an obscure case, to school the patient thoroughly in the mechanism of allergy so that his observations may be directed along useful channels. He should observe whether or not the origin or relief of symptoms bears any relationship to season, time of day, geographic situation, local environment, the proximity of animals or fowl, the eating of food, the use of cosmetics, wearing apparel, odors, habits, etc. Important information can often be gained through careful observation by the patient, which makes a correct diagnosis possible.

I may mention the history of a woman who was subject to asthma while in her own house, but was relatively free of asthma in other localities. She gave a positive skin reaction to an extract of dust taken from her vacuum cleaner. She remembered, then, that her asthma, of four years' duration, dated from the purchase of new furnishings for her house, among which was a large rug. The rug was thoroughly cleaned with a vacuum cleaner, and saline solution was allowed to filter through it six times. The solution was then filtered through a stone filter, and injected intracutaneously. A marked local reaction and an attack of asthma immediately followed. Disposal of the rug resulted in an immediate cure. The patient was not sensitive to wool or other animal hair, nor to extracts similarly made from other articles about her house.

Symptoms which appear only in the spring, summer or fall, or bear a relationship to geographic situation are usually traceable to plant life

# SPECIFIC TESTS IN THE DIAGNOSIS OF ALLERGY

W W DUKE, M D

KANSAS CITY, MO

There are few subjects before the profession today more interesting and important than specific hypersensitiveness. The condition is common and afflicts perhaps 12 to 15 per cent of adults.

Several sources of information are useful in the diagnosis of hypersensitiveness. From them, one can usually discover not only whether or not a given illness is fundamentally allergic in origin, but also what the specific allergen responsible for the illness may be. These sources of information are (1) family history, (2) personal history, (3) examination, (4) observation by the patient, and (5) specific tests (cutaneous, ophthalmic, nasal, subcutaneous, clinical, etc.).

Each source of information is important and depending on the case, one may be more important than the others. For this reason, each will be discussed in some detail.

## FAMILY HISTORY

Specific hypersensitiveness is one of the most consistently hereditary of diseases. In outspoken cases, a positive history of the condition in one or both parents can be elicited in almost 50 per cent of cases. Cooke and Adkinson each report an antecedent history of allergy in 48 per cent of cases studied. Each also found that with a positive history in both parents, the disease appeared at an earlier age than when it obtained in one parent only. A positive family history, therefore, is very important confirmative evidence in the diagnosis of allergy.

## PERSONAL HISTORY

A number of symptoms are characteristic of allergy. Worthy of especial mention are the ocular (edema of the conjunctivae, puffiness, redness, swelling and itching of the lids, and increased lacrimal secretion), the nasal (sneezing, pallor and swelling of the mucous membrane of the nose, associated with watery or clear mucous secretion), the pharyngeal (itching of the soft palate and pharynx, and cough), the bronchial (bronchial obstruction associated often with wheezing and the expectoration of clear mucoid sputum rich in eosinophils—in lighter cases, cough and shortness of breath on exertion), and the cutaneous (urticaria, angioneurotic edema, eczema, erythema, pruritis). Much less characteristic are the gastro-intestinal symptoms (abdominal pain,

entirely by clinical tests because the patient gave delayed reactions in each case and was sensitive to two common articles of diet. After the offending allergens were discovered through the use of cutaneous tests, the patient was able to obtain complete relief by their avoidance. The diagnosis was then proved by the fact that thereafter the patient could bring on a typical attack of asthma by the ingestion of a small amount of either milk or egg. The symptoms never appeared sooner, however, than thirty-six hours after either the intracutaneous injection or the ingestion of the offending substances.

#### SKIN TESTS

Two methods of making skin tests are used at the present time, the cutaneous or scratch method, advocated particularly by Walker, and the intracutaneous, advocated by Cook and others. Both have a sphere of usefulness. The intracutaneous, the more delicate method, gives a far greater number of positive reactions than the cutaneous, but has the disadvantage of giving a greater number of false positive reactions, or, rather, giving a greater number of positive reactions in patients who are not clinically sensitive. This is no great handicap, if the results are taken for what they are worth and what they actually indicate, and are used only in conjunction with information gained by history, physical examination and special tests. In this case, they are valuable, and rarely lead to serious error. The cutaneous reactions (or scratch tests) have their greatest sphere of usefulness in the testing of children and of patients sensitive to pollen and other air-carried allergens. Patients of these types respond readily, as a rule, to cutaneous tests. Scratch tests are useful also for testing patients sensitive to agents such as turpentine, benzol, and other substances which might prove irritating or harmful if injected intracutaneously. Cutaneous tests often fail utterly in older individuals and in patients whose symptoms appear to occur as a result of a general reaction, as in food cases. In these, intracutaneous tests often give marked and convincing reactions.

In our experience, both the cutaneous and the intracutaneous methods are useful, and neither should be used altogether to the exclusion of the other.

#### METHODS OF MAKING TESTS

Methods of making tests are described in some detail because, in this work, relatively simple and at the same time relatively accurate methods are almost essential if this sphere of knowledge is to be used broadly by the profession, as is also liberality in the interpretation of results obtained.

(usually to pollen, less often to emanations from the bloom, leaves or stalk) Symptoms which bear a relationship to local environment, such as house or work shop, are usually traceable to dust or some article or animal in the house. Among dentists, eczema or asthma is frequently traceable to sensitiveness to cocain, procain or apothecin. An undertaker whom we examined was sensitive to formaldehyd, a patient, subject to chronic asthma, worse in her own home than elsewhere, had a severe attack after the painting of her house and was proved sensitive to turpentine, another subject for several years to nasal allergy, proved sensitive to orris root. She was relieved after discarding cosmetics, and especially after dispensing with a sachet which she kept in her dresser drawer. Occasionally, it seems impossible to discover the specific allergen responsible for house allergy, and one of our patients has had to give up his business on this account.

Symptoms which bear a relationship to stables are usually traceable to an animal, occasionally to emanations from vegetable matter, such as hay. Symptoms which bear a relationship to city or railroad cars are often traceable to smoke, to farms and country, often to plant life, to time of day, usually to an article with which habit brings the patient in contact. Night asthma is often due to house dust, wool or feathers. Asthma of any sort, whether of cardiorenal, emphysematous or allergic origin, is inclined to be worse at night.

Symptoms which follow the eating of certain meals are often traceable to an article of food, if the symptoms appear frequently, to a common article of food, and if rarely, it is an unusual article of diet.

Often the working out of an obscure case depends as much on detective work as on the persistence of the physician, and success can occasionally be attained only by visiting the patient's home or shop, and making careful observations.

#### SPECIFIC CLINICAL TESTS

Useful crude clinical tests can often be made by having a patient eat a suspected food, or inhale a suspected vapor or the odor of suspected perfume, or the emanations from fur, feathers, animals, etc., or by the application of suspected substances to the skin, etc. Such tests often make a correct diagnosis possible in the easiest sort of way. Frequently, however, this method of testing presents difficulties. In a person who is sensitive to several articles of food, such as milk, eggs, and certain vegetables, the greatest persistence in eating or in avoiding certain foods may fail utterly to give the diagnosis. This is especially true when reactions are delayed. In one patient with asthma who had been treated by several careful physicians, the primary sources of the disorder (which proved to be both milk and egg) were missed

experience, more than six years), while solutions tend to deteriorate rapidly unless kept at icebox temperature. For this reason, potent allergens in the form of powders can be dispensed by commercial chemists and can be kept indefinitely, thus relieving the practitioner of the laborious process of repeatedly making and standardizing his own solutions.

That this method can be criticized as rather inaccurate is admitted. It is inaccurate, but no more so than any cutaneous (or scratch) method. Inaccuracy in the scratch method lies in the fact that the quantity of allergen absorbed by the skin is an unknown factor, as is also the strength of the solution formed after the mixing of powder and solution on the skin. Methods of testing cutaneously or intracutaneously are of necessity inaccurate in many cases. We often have no knowledge whatever of the substances with which we test our patients and to which they react.

I may mention the case of a physician who was subject to abdominal seizures which I suspected were allergic in origin and due to the occasional use of acetylsalicylic acid. On account of the physician's statement that he often took acetylsalicylic without ill effect, we tested him intracutaneously with five different brands. He gave negative reactions with four and an intensely positive reaction with one. Further than this, he was able to provoke an abdominal attack with the preparation to which he gave a positive cutaneous reaction, while the others caused no ill effect. He was evidently sensitive to some impurity contained in the one preparation. The impracticability of standardizing such an impurity for use in cutaneous testing is self-evident.

In citing this case, I do not wish to be taken as advocating inaccurate methods when accurate methods can be used. I simply advocate inaccurate tests rather than no tests at all.

One frequently wishes to test a patient with some substance for which he has no stock solution, such as a certain variety of straw, clover, newspaper, a dress, carpet, upholstery and dust. Suitable extracts of such substances can often be made by allowing them to stand several hours in a solution such as described by Wodehouse and Olmsted, or in Coca's solution, and filtering for the sake of sterility through a Berkefeld filter. It is usually impossible to standardize a solution of this sort since the offending element is an unknown quantity.

It is hardly necessary in a paper of this scope to describe in detail the methods of preparation of solutions of the different types, since this has been admirably done in a recent article by Coca and by Wodehouse and Olmstead. It may be well, however, to mention the fact that in making a preparation for cutaneous testing one should endeavor to obtain the suspected substance in relatively concentrated form. If an individual is thought sensitive to emanation from clover, the extract should be made of the whole, unbruised stem, leaf, or flower, the idea



By Walker's cutaneous method, the foreign materials in dry powdered form are applied to scarified areas on the skin, and to this is added a drop of tenth normal sodium hydroxid solution. The appearance of a hive, with pseudopods surrounded by an irregular area of erythema, indicates a positive reaction.

Cook and his associates use standardized solutions in varying strengths and inject intracutaneously 0.01 c.c. The appearance of a hive, with pseudopods and erythema, indicates a positive reaction. Small reactions without pseudopods are disregarded. This method, while technically difficult, is very useful, especially in patients whose skin does not respond readily to cutaneous tests. The difficulty in technic does not lie in the injection of the solutions but in the preparation of solutions for testing. At the present time, it necessitates a physician's repeatedly making and standardizing several hundred stock solutions of his own. This can be handled practically only in well organized laboratories.

During the last year, I have used a method similar to Cook's, but in previous years, I used one which was much simpler in testing for sensitiveness to food proteins. It is not so accurate as Cook's, and is not adapted to testing for sensitiveness to pollen and other air-carried allergens because of the solution being too concentrated. It is useful for physicians who make tests on only a few patients a week.

#### SIMPLE PLATE METHOD

About 0.1 mg. of each of the suspected substances (in dry powdered form) to be used in the tests is placed on a large sterile plate. One-tenth mg. of a powdered protein can be guessed at crudely as the amount of powder which can be taken up easily on the end centimeter of a sterile Peerless round wooden applicator. To each protein, 0.1 c.c. of physiologic sodium chlorid solution (distilled water will not dissolve globulin) is added. The first solution to be used is stirred and drawn up in a tuberculin syringe provided with a small needle. Then 0.01 c.c. of the solution is injected intracutaneously. The syringe is washed carefully in each of three separate vessels containing sterile physiologic sodium chlorid solution. The syringe can then be used for injecting allergen No. 2, and so on, if the syringe is washed thoroughly, and if the vessels of salt solution are always used in the same rotation.

Fontaine has suggested the use of 0.1 mg. tablets of allergen instead of the powders as used above. This modification reduces the limit of error, and also is easier to carry out. For physicians who test out a number of patients daily (from five to ten), the use of stock solutions is much better and can be accomplished by dissolving 1 mg. powders or tablets in rubber stoppered phials containing from 1 to 3 c.c. of Coca's solution or sterile physiologic sodium chlorid solution to which has been added phenol 0.5 per cent. as a preservative.

The advantage of this method lies in the fact that allergens in the form of a powder keep potent indefinitely if dry (according to my

allergens. In the group tests, it is advisable to use less of each individual allergen than in the making of individual tests. I use no more of the mixture than of the individual solutions in the final tests.

Preliminary tests made in this way often enable one to say that a patient is sensitive to a certain mixture of vegetables, grains, animal dander, sea foods, etc. Further tests can then be made with each allergen contained in the mixture giving positive reactions, and frequently a great deal of time and trouble for the patient can be saved.

No hard and fast conclusions can be drawn from preliminary group tests. It is simply a useful means of getting a clue. One often finds that a group reaction comes out more strongly positive than tests with any individual member of the group, and vice versa. One should not let a negative group test interfere with his trying any individual constituent of a mixture should he suspect it as a cause of illness.

Cooke has very properly warned against the use of a large number of tests at one sitting. We have employed the method described above for more than two years, using usually more than 300 allergens at one sitting. We have had a few severe constitutional reactions, but have not had an alarming reaction. We have been very careful, however, with certain cases, especially pollen cases during the pollen season. The use of a large number of allergens to which a patient does not react should have little or no ill effect.

Before leaving this subject, one should again warn of the danger of violent constitutional reactions which occasionally follow intracutaneous injections. One should have epinephrin and atropin on hand ready for quick use, and should use it immediately and freely if coryza, asthma, generalized erythema or itching of the skin develops. Patients should not be allowed to leave the office sooner than one half to one hour after the tests are completed and should then be warned of the possibility of a reaction appearing even later.

#### ONE SYRINGE METHOD

It is rather impracticable for the profession generally to use a large number of syringes and needles in making intracutaneous tests, and it is unnecessary. In our work, we use one syringe and one needle. After making an injection, we wash it thoroughly in each of three vessels containing sterile salt solution. The first vessel dilutes the allergen greatly, the second more yet, and the third to such an extent that any trace which remains in the syringe is too dilute to interfere with the accuracy of subsequent tests. The third water is not contaminated sufficiently to interfere with the use of the same three solutions for further washing of the syringe, that is, if the three vessels are always used in the same rotation. If one wanted to be

being to get in solution a maximum quantity of the substance contained in the outer part of the plant. In the case of food hypersensitiveness, the inner portion of the article is likely to be as important as the outer, so that maceration before extraction is desirable. One must add here that efforts at purification of any extract are usually inadvisable. Purification would be the logical thing if one knew the particular constituent responsible for illness. When an individual is sensitive, however, to a substance such as grain, it is impossible to surmise at the outset what substance is primarily responsible, and in the process of purification the real offender might be lost.

While purification of an extract is, in general, inadvisable, the use of purified extracts often gives useful information in the case of common foods, such as eggs, milk or wheat, that is, foods which are used so frequently in cooking as to be difficult to avoid. In the case of egg, if a person is proved sensitive to either egg white or egg yolk protein alone, the offending substance can be removed mechanically, and the remaining portion of the egg can be used. Furthermore cooked egg (coagulated protein) in this case may be tolerated. This information may enable a person to use cooked egg, cake, coffee in which egg is used in the clearing, etc., so that the avoidance of egg becomes no real hardship. In the case of ovomucoid, which is not coagulated by heat, it is necessary for the patient to avoid not only raw egg but cooked egg as well, in fact, occasionally, every food which contains even a trace of cooked egg. Likewise in the case of proved sensitiveness to lactalbumin, the milk may be rendered harmless by such a simple measure as boiling, while sensitiveness to casein may necessitate the discarding of milk altogether. Patients sensitive to certain raw foods are very often insensitive to the foods when they are thoroughly cooked. A knowledge of this may be a great convenience in choosing a diet.

Pollen allergens and some of the animal danders and other air-carried allergens should not be handled so promiscuously nor in the same concentration as food allergens. These allergens are, as a rule, stronger, they provoke more severe reactions, and they give convincing results when used in more dilute solution. Pollen extracts of a strength of 0.01 mg. of dry pollen to each cubic centimeter is usually concentrated enough to give marked reaction, in sensitive individuals. In group testing, usually 0.001 + mg. to the cubic centimeter of each individual pollen is adequate.

#### PRELIMINARY GROUP TESTS

The procedure of intracutaneous testing can be shortened and simplified somewhat through the use of preliminary group tests, that is, through the use of mixtures of from five to eight closely related

As regards the fact that patients proved sensitive to a given substance may give negative intracutaneous reactions, I believe, without compiling accurate statistics, that this condition is encountered more frequently in older individuals than in children, also, more frequently in individuals whose symptoms occur as a result of a general reaction than in individuals sensitive to air-carried allergens. A negative reaction is found more often in patients who have asthma, hives, or angioneurotic edema caused by ingestion of egg (general reaction) than in patients who have hay-fever or asthma caused by local contact of the respiratory mucous membrane with pollen or emanations from animal hair, etc.

In searching for an explanation of this fact, it might be mentioned that patients sensitive to a food can be sensitive to the food as it exists in a natural state or to some product elaborated during its digestion or putrefaction in the alimentary canal, or to some product formed by the parenteral alteration of some of its products after absorption. A patient with egg urticaria may be insensitive to egg but sensitive to a product formed from egg after many catabolic and anabolic processes. I observed a patient with egg asthma who gave a very slight skin reaction, but who was clinically so sensitive to ovomucoid that three drops of a solution of whole fresh egg made by diluting one drop of fresh mixed egg with 200 c c of water was sufficient to cause severe asthma, if taken by mouth. The same result appeared after the subcutaneous injection of 0.0001 mg of whole egg. The reactions produced in either way did not appear sooner than thirty-six hours after the treatment with egg.

The mere fact that the nasal mucous membrane or gastro-intestinal mucous membrane is sensitive to and reacts to a given substance does not necessarily mean that the skin is sensitive and should react positively. It is simply good fortune that the skin does react positively so often.

Given the facts that a negative skin reaction does not exclude a given substance as a cause of illness and that a positive reaction, although indicating sensitiveness to the substance, does not indicate that it is a cause of illness, the following general rules are of value in interpreting results.

- 1 Occasionally, the skin reacts to one substance only. When this is the case, the real offender, as a rule, is discovered.

- 2 The skin usually reacts to several substances and often to several groups of substances. When this is the case, the larger wheals usually indicate the real offenders. This is not invariably so. A patient may react markedly to vegetables and slightly to grains and be made actually ill by a grain only. The fact that extracts prepared for cutaneous

more careful, he could do so by using four or five vessels of salt solution instead of three. This is unnecessary, however, if one is thorough in his washings. I frequently find one test intensely positive and the next negative, proving thus that the cleansing of the syringe must have been adequate.

#### INTERPRETATION OF CUTANEOUS TESTS

One's first impression of intracutaneous testing is likely to be one of disappointment. If he is so unfortunate as to be seriously misled by them, the first impression may be one of disgust. The fault lies more often, however, in the interpretation of results than in defects in the method itself.

In order to interpret correctly it is necessary to bear in mind two facts: (1) that a strongly positive intracutaneous reaction with a given substance does not necessarily indicate that it is responsible for an illness, and (2) that a negative reaction with a given substance does not exclude it as a cause of illness. A positive reaction, excluding those which occur as a result of traumatizing a skin rendered unusually sensitive by allergy, indicates simply that the skin is sensitive to a given substance when given intracutaneously. It does not indicate that the patient is sensitive to the substance as encountered in natural ways. In other words, the patient, although actually sensitive, may tolerate the substance as encountered naturally, and in the dosage encountered naturally.

One patient subject to no apparent illness, except autumnal hay-fever, gave intensely positive intracutaneous reactions to each of about twenty spring and fall pollens, to several specimens of animal hair, and to several proteins extracted from fruits, vegetables and grains. He was ill, so far as one could judge, only in the fall, and could relieve himself by a change in geographic situation. He was evidently sensitive to many substances, but his tolerance was such that none except fall pollen as encountered in his mode of living made him ill.

A somewhat different type of case is that of a patient with active tuberculosis who was subject to asthma, regardless of season or geographic situation. She gave positive skin tests to wheat. Avoidance of wheat in the diet gave her no relief whatever, but avoidance of contact with flour (inhaled while making bread) gave her great relief, even when she ate wheat bread freely.

This finding might be explained in several ways. It is possible that the nasal mucous membrane was intolerant of wheat flour when inhaled, but was tolerant of the small amount reaching it through the blood stream after the ingestion of wheat. It may have been, on the other hand, that the flour was so changed by cooking or by digestion that the product to which she was actually sensitive was destroyed. It is well known that patients sensitive to lactalbumin (a protein of milk coagulable by heat) who are made ill by small amounts of raw milk can tolerate often almost unlimited quantities of boiled milk.

secretion which persists for several minutes or more. The ill-effect of this reaction can also be relieved by the local use of epinephrin.

These tests are especially useful in pollen cases, and with their aid one can often pick out from a group of pollens which give positive cutaneous tests the one particular pollen responsible for clinical symptoms.

In a patient who gave positive intracutaneous tests to almost every fall pollen which was used in testing, *Artemisiaefolia* was the only one of the group which caused a positive ophthalmic reaction. She was treated with *Artemisiaefolia* extract for several months before the hay-fever season began and was apparently rendered so tolerant of this pollen that, although she continued to give a positive skin reaction to it, she had no symptoms of hay-fever during the entire season. The inference might be drawn in this case that, although she was sensitive to many pollens before treatment, tolerance for all except *Artemisiaefolia* was such that she could stand without difficulty the amount encountered naturally in her ordinary habits of life.

Ophthalmic and nasal testing is limited in usefulness because relatively few tests can be made on a patient in one day. A positive reaction prevents further use of the eye for testing for a day or two. A negative reaction does not interfere with further testing, and often if one suspects one of a group of, say, six different pollens, the entire six may be tried, provided the ones which give the positive reactions are used last.

Patients who are clinically sensitive to a pollen usually react positively to a 1:1,000 solution. Occasionally, they do not. It is possible that stronger solutions might be used in an effort to provoke a positive reaction. We have not studied this point, since a majority of patients do react to the solution as described. It is not out of line with our knowledge of facts that patients who fail to react to a 1:1,000 solution of a given pollen extract can be actually clinically sensitive to the pollen as encountered in nature. It must be borne in mind that during the pollen season, the conjunctivae encounter pollen dry and untreated. It is not difficult to conceive that the exposed tissues may react to dry untreated pollen even though insensitive to pollen in high dilution.

Nasal tests are also useful for testing in a simple way for sensitiveness to animal hair, feathers, or emanations from vegetable matter, etc. The test can often be made by having the patient inhale from the substance to be tested and noting whether or not it causes sneezing or other symptoms resembling hay-fever. I obtained a very convincing reaction in a carpenter who was troubled with nasal and bronchial allergy while in his work shop. He had a violent attack of sneezing when asked to inhale from a bag of birchwood shavings. The inhalation from shavings of seven other woods caused no symptoms whatever. It is often possible to get reactions of this sort with feathers or furs, or sometimes with solutions such as perfume, cedar oil, turpentine, smoke and like substances.

testing contain a large variety of chemical bodies may account for this circumstance. The allergen responsible for an illness may be the largest constituent of the mixture or the smallest constituent. If the offending allergen is the smallest constituent, the skin reaction may be less marked than that produced by mixture containing a less offensive allergen in larger amounts. It may be mentioned again that marked skin sensitiveness does not necessarily indicate marked sensitiveness to the substance as encountered naturally.

A woman who had been subject for months to almost daily spells of abdominal pain and vomiting, was emaciated and seemed unable to tolerate any type of diet which was chosen for her. She gave positive intracutaneous reactions to almost every type of food, although to some much stronger than others. After many combinations of food in the diet had been tested without benefit, she was put on a diet confined to meats and fruits. She was absolutely free of symptoms while on this diet and gained, in a short time, over 40 pounds (18 kg) in weight. Many attempts were made to add to the diet but without success. The least digression caused immediate recurrence of vomiting and pain. Milk and eggs, which did not give strong skin reactions were not tolerated even when taken in small amounts.

Although the foregoing facts may be disturbing to those enthusiastic over the possibilities offered by cutaneous tests, they are less disturbing than error, and if one bears in mind the fact that positive skin tests indicate sensitiveness only to an allergen as applied in the test and not necessarily sensitiveness to an allergen as it is encountered in nature, one can often gain many useful clues without being seriously misled. A clue gained from a skin test should never be looked on as diagnostic but should be used as a clue only. The diagnosis should be verified by and based on history and examination, and on other tests to be mentioned subsequently.

#### OPHTHALMIC AND NASAL TESTS

The ophthalmic and nasal tests are especially useful in picking out pollens or other air-carried substances responsible for hay-fever and asthma. These tests should be made after the results of intracutaneous testing have been observed. The ophthalmic test is made by spraying pollen solution (1 1,000 extract from dry pollen) into the conjunctival sac. A positive reaction is indicated by redness of the conjunctiva and increased lacrimal secretion which persists for more than five minutes. Momentary redness cannot be considered positive. The effect of a positive reaction may be immediately relieved by instilling a drop of epinephrin (1 1,000 solution) in the conjunctival sac.

The nasal test is made by spraying a pollen solution (1 1,000 solution) into the nose. A positive reaction is indicated by sneezing, swelling of the nasal mucous membrane, and watery or clear mucous

condition is not self-evident, the diagnosis should not be based on one series of facts but on several. If allergy is the suspected cause of an obscure illness, a positive family history or a history of other typically allergic symptoms in the same individual is important confirmative evidence. Cutaneous tests, subcutaneous tests and other specific tests are of additional value.

The diagnosis should rarely be considered conclusive, however, until the allergen responsible for the illness is found and removed, with relief to the patient, and finally confirmed further, if possible, by the reproduction of the illness during a well period by the patient's being again brought in contact with the suspected substance. These criteria are important. A great many secondary factors aggravate allergic symptoms in sensitive individuals and lead to error in diagnosis. Patients with pollen asthma are usually made worse by several other agents which have no untoward effect on them except in the pollen season. Patients with gastric allergy due to hypersensitiveness to egg will almost invariably be made worse by rough foods, such as popcorn or nuts, by irritating foods, such as paprika or mustard, or by foods which stimulate the secretory activities of the gastric mucous membrane, such as alcohol, salt or sweets, so long as the gastric mucous membrane is in a reactive state due to the ingestion of egg. If egg is removed from the diet, these foods may cause no ill effect whatever.

Secondary factors often mislead both patient and physician, and cause one to suspect them rather than the primary factor as the cause of illness. Infection augments the symptoms of nasal and bronchial allergy. Patients with mild bronchial allergy (not bacterial in origin) are usually much worse during and after an attack of bronchitis. The organism responsible for the bronchitis might easily be suspected as the primary cause of the disorder, but when the allergen responsible for the condition is found and removed, further attacks of bronchitis amount to nothing more than slight cough of short duration.

Functional and organic diseases, as well as infectious diseases, can modify the symptoms of allergy and mislead a physician, as can reflexes also. Patients with asthma may be made either better or worse by eating a meal, by a movement of the bowels, taking an emetic, by changes in barometric pressure, temperature, or dryness of the atmosphere, or even by pressure or change of pressure in the nasal sinuses. These facts, while relatively simple to read, may be most misleading unless one is strict in establishing his criteria, and bases his final conclusion, not on one line of evidence, but on every line which is at his disposal.

#### SUMMARY AND CONCLUSIONS

Specific hypersensitiveness may be suspected in any person who has in his family or personal history, or who on physical examination



One must carefully discriminate between patients who are actually specifically hypersensitive to a substance of this kind, and those who have a nasal allergy due to other causes and who give a positive nasal reaction due to the nonspecific irritating effects of the substance used in the test. Patients with pollen asthma will frequently be made to sneeze or to suffer an aggravation of their symptoms if they inhale perfume, smoke or dust. The inhalation of these substances, however, may have no untoward effect on them except during the pollen season. In other words, though made worse by their inhalation, these patients may not be actually specifically hypersensitive to them.

#### SUBCUTANEOUS TESTS

Subcutaneous tests have their greatest sphere of usefulness in confirming a given diagnosis. If one suspects *artemesiaefolia* as a cause of hay-fever, and can inject a small quantity of *Artemesiaefolia* pollen extract subcutaneously during a well period and reproduce the symptoms of hay-fever, he should feel convinced that *Artemesiaefolia* is the probable cause of illness. Similarly, if one believes sensitiveness to milk is responsible for abdominal pain or bladder disorder, and can reproduce these symptoms during a well period by subcutaneous injection of milk, he should feel that he is on the right track.

In order to prevent severe constitutional reactions, subcutaneous tests should be used with great care, and only minute amounts should be injected. If one suspects lactalbumin as a cause of asthma, not more than 0.0001 c.c. of lactalbumin should be given subcutaneously as an initial dose. If this should fail to produce asthma, a larger dose might be administered. The ill-effect of a reaction can be combated almost immediately, as a rule, by the subcutaneous injection of 0.5 c.c. of epinephrin (1:1,000 solution). If there are no signs of relief within two or three minutes, 0.25 c.c. doses can be repeated at from two to five minute intervals until relief is obtained.

The sensitiveness of some patients to foreign materials is extraordinary, and anyone dealing with this subject should bear this fact in mind. One person with asthma whom I observed was so sensitive to wood smoke that the application of a drop of Wright's concentrated wood smoke to a scratch on the skin produced not only a wheal which reached from shoulder to elbow, but also asthma, coryza, erythema of the skin and a general reaction, which necessitated the hasty use of several doses of epinephrin.

#### DIAGNOSIS

In a relatively large proportion of cases of allergy, the diagnosis is apparent, and can be made by history and physical examination (pollen hay-fever and asthma, for example). In obscure cases, in which the

## THE MECHANISM OF PRODUCTION OF BREATH SOUNDS

P MARTINI, M D

MUNICH, GERMANY

Since Baas<sup>1</sup> proposed the theory that vesicular breathing was only modified bronchial breathing, two different opinions have prevailed as to the origin of the breath sounds. According to one theory, the specific vibration of the porous tissue of the lung put in motion through respiration causes vesicular breathing, the second theory, like that of Baas, maintains that the vibrations of the bronchial system alone force their specific frequency on the tissues of the lungs and on the chest wall, respectively, being there either weakened or strengthened, according to the physical conditions of the vibrations of the air and of the conducting tissue of the lung. To the latter process, the laws of the so-called forced vibrations, as first proved by O. Frank,<sup>2</sup> should be applicable. These laws may be of interest.

1. A correct conduction of the sound is possible only if the specific sound and the specific frequency,<sup>3</sup> respectively, of the conductor of sound (for instance, of the tissue of the lung) are of a higher pitch than all the partial tones of the sound to be conducted.

2. If partial tones of the sound to be conducted are higher pitched than the specific sound of the conductor, they will be considerably weakened.

3. If some are lower, they will be conducted correctly.

4. If a partial tone of the sound to be conducted and the specific sound of the conductor attune in their pitch of tone (frequency per second), resonance may result.

If these laws are to be applied to the problem of auscultation, the kind of motion of the tissue of the lung, both air-bearing and solidified, which serves as a conductor of sound, both of the air-bearing tissue

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\* From the II Medical Clinic (Friedrich von Muller) of the University of Munich.

1. Baas. *Deutsch Arch f klin Med* **69**.

2. Frank, O. *Ztschr f Biol* **53**, **56**.

3. The pitch of the proper sound of a body increases with its firmness, it decreases with its size. The pitch and frequency of sound and the frequency per second are proportional.

shows, certain rather typical manifestations of the condition ocular, nasal, pharyngeal, bronchial or cutaneous symptoms. It may be suspected in patients who show certain less characteristic symptoms, if no other adequate cause for the disorder is found on examination the gastro-intestinal, and bladder symptoms, headache, nervousness, asthenia, hypotension, etc. The foregoing symptoms suggest the possibility of allergy, especially when they occur in the absence of other adequate cause for illness, and when the family or personal history is positive.

In searching for the source of allergy, or rather for the specific allergen primarily responsible for an illness, careful observation by the patient is helpful and often makes complete study and a correct diagnosis possible.

Specific tests are often useful in gaining a clue as to the source of allergy. The cutaneous tests are useful in young persons or in persons sensitive to air-carried allergens. The intracutaneous are more useful in the less sensitive persons, i. e., older patients, those sensitive to foods, and those whose symptoms occur as part of a general reaction. Intracutaneous tests often result in positive reactions in patients who are not sensitive to the allergen as encountered in nature, and, vice versa, persons who are sensitive to certain allergens as encountered naturally do not always give positive intracutaneous reactions. For this reason, care should be used in the interpretation of skin tests, and a diagnosis should not be based on the results of these tests alone. These results should be used as a clue only and should be verified by other special tests, such as the nasal and ocular tests, or subcutaneous or clinical tests.

Many secondary factors modify the symptoms of allergy, such as infectious disease, functional or organic disease, reflexes, agents which irritate or stimulate either mechanically, chemically or otherwise, so that a diagnosis should be based, if possible, not only on the history of a case and physical examination but also on the apparent finding of the specific allergens responsible for an illness, on removal of the allergen with relief of symptoms, and, finally, on reproduction of symptoms during a well period by bringing the patient again in contact with the suspected substance. Few mistakes in diagnosis will be made when these procedures can be carried out fully, and conclusions can be based on adequate data.

plate) were registered (Fig 3) The plate did not predominate over the cavity nor the cavity over the plate, but the single parts of the entire system forced their specific vibrations reciprocally on each other By means of such drumlike systems the specific vibrations of one predominating system are not forced on the other, the one does not serve as a resonator to the other, but the specific vibrations of both parts are superimposed equally one upon the other

There is no doubt that the mechanism of the pneumothorax resembles closely that of the model just described But this is not the case in the same degree under other pathologic and under normal conditions Normal conditions may be imitated by filling the wooden box

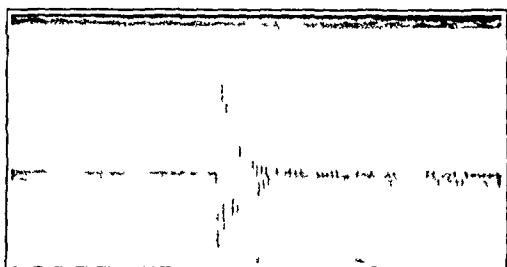


Figure 2



Figure 4

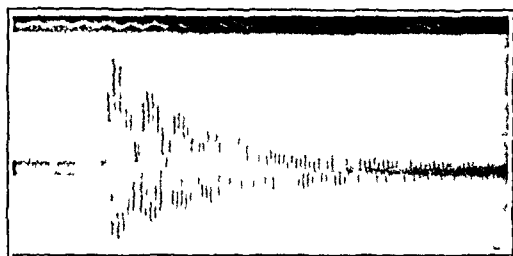


Figure 3

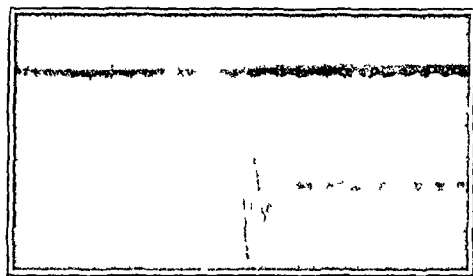


Figure 5

Fig 2—Specific vibrations of the plate

Fig 3—Vibrations of the cavity and plate in combination

Fig 4—Vibrations registered by model when normal conditions were imitated

Fig 5—Vibrations shown when model approaches pathologic conditions Registration shows only vibration of wall, the vibration of the contents has completely disappeared

with a porous tissue, such as cellulose When we did this, two separate vibrations were distinctly registered (Fig 4)

The model approaches the pathologic conditions if filled with moist cellulose, thus corresponding to massive consolidation In this case, the registration shows only the vibration of the wall, while the vibration of the contents has completely disappeared (Fig 5) The mass of the contents being greatly increased, its sensibility is consequently much diminished, so that there can no longer be periodical vibrations

and of the solidified one must be clear. Furthermore, we should be clear about the origin and the qualities of the vibrations originating in the laryngobronchial system.

The first task leads to the problem of percussion, the mechanism of which has been investigated for many years at our clinic under the guidance of Dr. Friedrich von Müller<sup>4</sup>. We believe that we have finally succeeded in solving this problem experimentally. The mechanism of percussion bears a great resemblance to the beating of a drum. In both cases a thin wall or membrane is struck, behind which is a medium capable of complicating the specific frequency of the wall. Several authorities have already referred to the great importance of the drum theory in connection with the question of percussion, but up to the present time there has been no agreement. Either too great importance was ascribed to the wall for the formation of the tone, leaving to the cavity no function but that of a resonator (the natural philosophers, chiefly, were of this opinion, and recently Bushnell

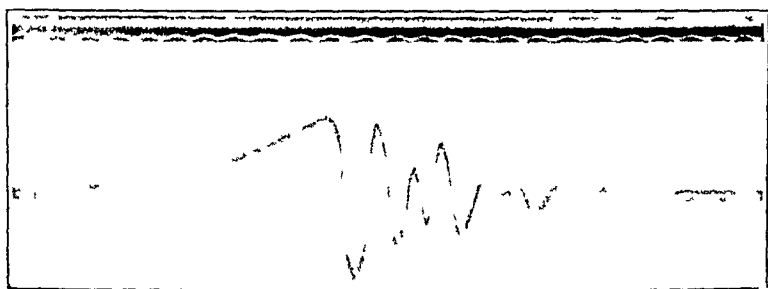


Fig. 1—Specific vibrations of the cavity

expounded this theory<sup>5</sup>), or it was thought that only the cavity is of importance for the pitch of tone, while the membrane only renders the transmission of the waves of the sound to the atmosphere more or less difficult. The majority of physicians believed the latter.

In order to solve the problem a model was required, the parts of which could be observed both singly and in combination. For this purpose, I constructed a cube-shaped wooden box with strong walls and open on one side, this side could be closed with a wooden plate replacing the membrane of the drum. By means of this box the problem was solved graphically.

At first the specific vibrations of the plate and of the cavity were registered separately, whereby typical curves were produced by both (Figs. 1 and 2). Then the vibrations of the closed system (cavity plus

4 Müller, Frederic von. *Verhandl. d. d. Kongr. f. inn. Med.* 1911, *Ztschr. f. arztl. Fortbild.*, 1912. Lelling, T. *Arch. f. klin. Med.* **90**. Edens and Ewald. *Arch. f. klin. Med.* **123**. Martini, P. *Arch. f. klin. Med.* **139**.

5 Bushnell, George E. The Mode of Production of the So-Called Vesicular Murmur of Respiration, *J. A. M. A.* **77** 2104 (Dec. 31) 1921.

from the vibrations of the wall. Finally, I registered also the note of percussion of the thorax with completely solidified lung (Fig 8)

In accordance with the experience obtained by filling the wooden model with moist cellulose, no sound of the lung is produced in this case. The completely solidified lung is mute, and what we hear above it on percussion is nothing but vibration of the chest wall. The specific frequency of the solidified lung cannot, therefore, be decided in this manner. So much for the physical conditions of the tissue of the lung, so far as percussion can give any information.

In auscultation, the solid part of the tissue of the lung is to be taken into consideration as a conductor of sound under normal conditions as well as in consolidation. The question is, Is this also to be considered in the origin of sound? For the solidified tissue we may promptly answer in the negative, because it will be just as mute as on percussion. For the air-bearing tissue we must, for the present, leave the question unanswered.

Now we must ask ourselves whether the air does not also come into consideration as a conductor of sound in the much ramified bronchial system of those portions of the lung that are chiefly solid, as mentioned above, or whether it is of importance only as a source of sound. The reply to this question depends on the explanation of the origin of the laryngobronchial breath sounds. I have fully explained in another journal<sup>6</sup> the reason why I do not believe that the vocal cords are of any importance for the origin of this sound, as Geigel has brought forward and Bushnell<sup>5</sup> has again affirmed. After the elimination of the vocal cords through entire paralysis or through a tracheoscope, the breath sounds show hardly any change. This result seems to me to be of much more importance than Bushnell attaches to it. Where else should the bronchial breathing originate after the elimination of the vocal cords through a smooth tube, such as the tracheoscope, if not in the tracheobronchial ramifications? And why should this mode of origin suddenly lose its value, when the tracheoscope, by the introduction of which these vibrations were not affected, is again taken away? That is what we should have to suppose if the sounds—well audible while the tracheoscope was introduced—were no longer audible without the tracheoscope with wide-open throttle, as stated by Bushnell. With wide gaping vocal cords I also always hear breath sounds over the trachea as well as over the lung when the respiration is rapid enough. I do not think that the glottis has an essential part in originating the bronchial breathing, but in my opinion this sound definitely arises from the edges and corners of the bifurcations of the trachea and bronchi.

There is no doubt that on percussion of the chest the wall and the contents are intimately associated. Under normal conditions, the vibrations of the wall will dominate over the vibrations of the contents still less than is the case with our model. Indeed, by the graphic registration of the human tone of percussion, only the specific vibrations of the contents could be registered, never those of the wall. This arose to some extent from the insufficiency of the method, but chiefly because of the minimal energy of the high tones of the chest wall. It was only in consequence of the exceptional and peculiarly partial conditions of sensibility of our ear that they often predominated so clearly in the subjective character of the sound.

With the help of graphic registration, we found over the chest of adults a fundamental note between G and C (from ninety-five up to 130 vibrations a second) (Fig. 6)

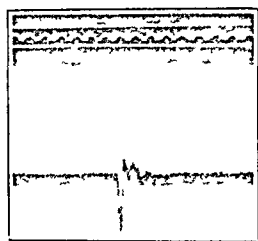


Figure 6

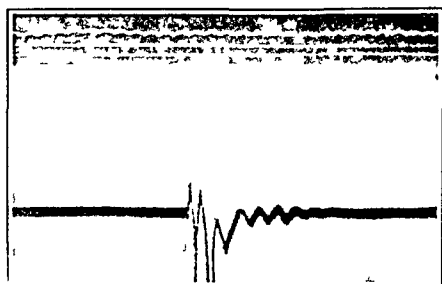


Figure 7

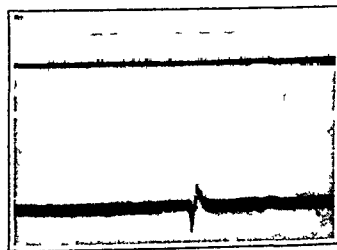


Figure 8

Fig. 6—Vibrations registered over the chest of adults

Fig. 7—Percussion of exenterated lungs when percussed by pleximeter

Fig. 8—Percussion tone of solidified lung

We found the note of percussion of the exenterated lungs to be of exactly the same pitch (Fig. 7) when percussed by means of the pleximeter.

Therefore, I am strongly inclined to contradict Bushnell,<sup>5</sup> when he says "that the sound of percussion, as it reaches the lung, contains the fundamental note," and that it is due to the resonance of the lung of this specific tone of the chest wall, which corresponds to its specific tone. The experiments with our model showed that the specific vibrations of the wall and of the cavity of the box, which are coupled with one another, are simply superimposed on each other. On percussion the same fundamental note was found, whether the lung is percussed directly or by way of the chest wall. This can signify only that the chest wall has little influence on the pitch of the vibrations of the lung and that the vibrations of the contents of the thorax are pure specific vibrations from the beginning, which have their own existence apart

According to Bushnell, the predomination of the high overtones of the bronchial breathing can only be explained on a two-fold supposition. First, Bushnell supposes that in bronchial breathing the bronchi, but chiefly the mouth and the nasopharynx, serve as resonators. This I must contradict, there is not reason why resonance should only be produced in these cavities in consolidations and not in normal conditions. In an earlier publication I have explained why I cannot also acknowledge resonance in the smaller bronchi as the original cause of the bronchial breathing, as Sahl<sup>1</sup> supposes it to be. And still less can it be conceded that, "in massive consolidations of any kind, the deep and medium-pitched tones are suppressed," or, in other words, that the solidified lung cannot give covibrations with the deep tones of the laryngeal sounds, as supposed by Bushnell. The well founded laws of forced vibrations are in absolute opposition to this, as has been our experience, telling us that even tones as deep as the low *c* (128 vibrations a second), which lie in the lower limit of the human voice, are better propagated through a solidified (infiltrated) lung (Fig 10*a*), than through an

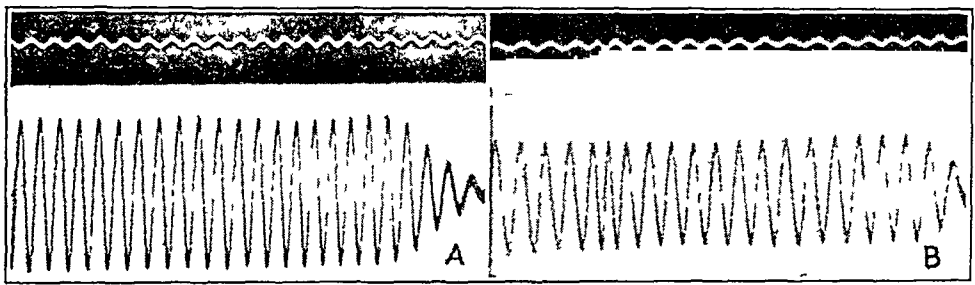


Fig 10—Registration of low tones propagated *a* through a solidified lung, *b*, through an air-bearing lung

air bearing (normal) one (Fig 10*b*). The bronchial breathing which is audible over solidified tissue, may rightly be considered, as a correctly propagated specific vibration of the air of the bronchial system.

Some time ago, by means of resonators, Dr Muller estimated the pitch of the bronchial breathing between  $d^2$  and  $d^3$ . With the same method, I found an upper limit of  $c^3$  (about 1,000 vibrations a second) and a lower one of  $d^2$  to  $e^1$ . In another paper,<sup>7</sup> I have stated why the results which are obtained through resonators can claim but limited validity. We tried, therefore, to register the bronchial breathing objectively from the chest wall and found pitches from  $e^1$  to  $d^2$  and from 300 to 500 vibrations a second, respectively, never lower ones. The periods were always regular, which was to be expected on account of the characteristic, almost musical sound. The conformity with the lower limit of reach of the bronchial breathing which was established by means of the resonators, is evident (Fig 11).



The larynx is therefore not the origin of the tone whence the sound vibrations are conducted to the periphery of the lung, but the whole tracheobronchial system down to the smaller bronchi is to be looked on as the origin. Under what conditions will this original sound, the specific sound of the air-filled bronchial tree, be clearly audible? Can we auscultate it unaltered? Of what kind of vibrations does it consist? In any event, we can be certain of observing the specific note of the bronchial system by itself, that is, without the addition of other sounds, only when the elimination of specific vibrations of the solid tissue of the lung is guaranteed. This is the case in massive consolidation, when, as can be shown, the solid tissue of the lung is completely mute. The site for auscultation of the vibrations taking place in this bronchial system has to be connected with a bronchus in solidified tissue by a correctly conducting tissue. The best way to ascertain the degree of capacity of a body is to observe by objective registration, if possible,



Fig 9—Registration of vowels and word sounds made by patients with massive consolidation of lungs into a registering apparatus, *A*, also sounds coming from a solidified lung, *B*, from a normal lung, *C*

how it modifies known tones and sounds in their passage through it. We made patients with massive consolidation speak vowels and words into a registering apparatus (Fig 9a) and, in addition, we registered the same sounds coming from the solidified (Fig 9b) as well as from the normal lung (Fig 9c). The results were curves such as we see in Figure 9c.

The figures show that the vowel "A", in passing through the lung, retains very well its characteristic high overtone of ca-1,000 vibrations a second, while it loses it completely when passing through the air-bearing lung. If, accordingly, the solidified lung is still a good conductor of tones of 1,000 vibrations a second, it will also be able to conduct correctly the specific vibrations of the bronchial system. Thus one hears through a solidified lung, which is laid on the trachea, the voice as well as the tracheal breathing, including their high overtones.

This also was shown graphically (Fig 12) Its vibrations are much more irregular than those of bronchial breathing, the fundamental frequency fluctuates incessantly between 100 and 200 vibrations a second, which is not astonishing because of its noisy character. Thus vesicular breathing is not only relatively, but absolutely, deeper than bronchial breathing. While these observations cannot be in accord with the supposition of entirely forced vibrations and of resonance, respectively, they leave no doubt that, besides the vibrations of the bronchial system, another factor is also of great importance in originating the inspiratory breath sound which is audible over the air-bearing lung. Only the specific vibrations of the tissue of the lung can be taken into consideration as such. Bushnell has hinted at the affinity between vesicular breathing and the normal note of percussion. He thinks that in either case the same resonator responds with its specific tone, in one case to the vibrations of the bronchial system, in the other to the vibrations of the chest wall. There is no doubt that an affinity exists between the two, but we consider the rôle of the lung in the origin of



Fig 12—Vesicular breathing

the percussion-sound and vesicular breathing more important than that of a resonator. We think that the percussion sound corresponds to the sound of a string which has been struck, while we might compare the vesicular murmur to the sound produced by a suddenly strained string. Both tones of the string are different in their color of sound, but their fundamental frequency is of the same pitch. We could assume the same of the suddenly distended and of the percussed lung, and indeed we have found that their pitches agree to a considerable degree. The pitch of the percussed normal lung lies between G and c and even the deepest partial tones, which are contained in the vesicular murmur, reach as far down as the deep G. This conformity of the fundamental frequency makes it probable that percussion and inspiratory tension are but two different methods of bringing the lung out of its equilibrium. The lung endeavors to recover this state of equilibrium, around which it vibrates periodically and with the same fundamental frequency, just as a violin string when struck and when suddenly strained gives different colors of sound, but the same fundamental tone.

As to the overtones, which are decisive for the harsh "bronchial" character of the bronchial breathing, the curves gave no evidence, because of the probability that the absolute intensity of the overtones was again very small, much smaller than might have been supposed judging by the subjective acoustic impression

Concerning vesicular breathing, Bushnell asserts that the physiologic (normal) breathing is only modified laryngeal breathing. I have attempted to prove that the latter is identical with bronchial breathing. We know now its pitch of tone—its fundamental tone reaches at the utmost to  $e^1$  (300 vibrations a second) and lower. We are also sufficiently informed about the specific frequency of the conductor of sound, in this case that of the air-bearing tissue of the lung. With regard to the height of pitch, it will coincide with the established pitch of tone obtained on percussion of the normal lung, consequently, in normal adults, it will lie between A and c (about 100 and 130 vibrations a second). Recently I have been able to define graphically the maxi-

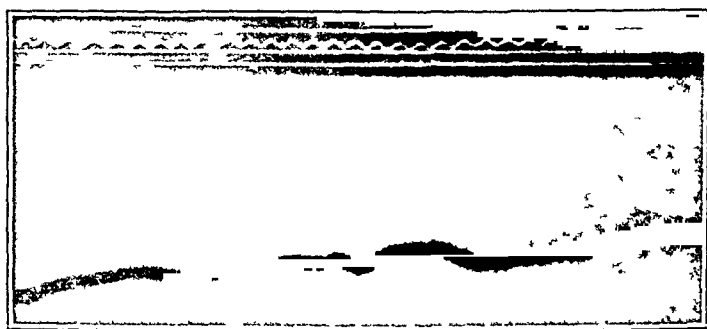


Fig 11—Bronchial Breathing

mum resonance of the lung. On the whole, it was found (working with men only, women's voices being too high-pitched) that the maximum always lay in the pitch of the sound of percussion (Fig 10a). Its quality as a specific tone of the lung was thereby newly affirmed. Also the frequency (pitch of tone) of the specific tone of the bronchi ( $c^1$  to  $d^2 = 300$  to 550 vibrations a second) was higher in each case than the specific frequency of the air-bearing, sound-conducting lung. In consequence of this proportion—according to the laws mentioned in the foregoing all specific vibrations of the system of the bronchi would be weakened while passing through the normal lung, the highest would even be extinguished entirely. A decreasing and relative, deepening of the breath sounds would follow. In reality this is observed when auscultating the trachea through an air-bearing lung. This explanation is not sufficient for the normal vesicular breathing heard over the human thorax. It will be eliminated by establishing the absolute pitch of tone of the vesicular breathing.

# SENSITIZATION TESTS WITH DIGESTIVE PRODUCTS OF PROTEIN '

I CHANDLER WALKER, M D, ARTHUR S WETMORE

AND

JUNE ADKINSON, A M

BOSTON

That sensitization to proteins occurs is well established. The only evidence so far produced is that it is the undigested protein that sensitizes and causes symptoms. Frequently, one meets with conditions the symptoms of which would seem to be due to protein sensitization, even though the protein tests are negative. For this reason it seemed to be advisable to try sensitization tests with the decomposition products of proteins in order to determine whether or not they might sensitize and cause anaphylactic symptoms when the whole protein failed to do so. The present work, however, would seem to show that the decomposition products do not sensitize human beings and do not play a part in human anaphylaxis.

We first attempted to digest egg white with normal human duodenal contents in order to simulate as near as possible normal digestion, but this experiment was a failure because of reasons noted below.

## DIGESTION OF EGG WHITE WITH HUMAN DUODENAL CONTENTS

The whites of a dozen hard boiled eggs were pressed through a potato ricer and then placed in a 2 liter flask with 1,500 c c of water. The contents were acidified with hydrochloric acid to approximately tenth normal, then 100 c c of fresh pig stomach extract was added and the mixture incubated at 37 C until the egg white was completely liquefied. Ten c c of this liquefied egg white was titrated with sodium carbonate, and then enough sodium carbonate was added to make the entire liquefied egg white approximately tenth normal alkaline. To this were added 100 c c of normal human duodenal contents, obtained by a duodenal tube, and the mixture was incubated two days at 37 C. At the end of this time a slightly modified protein was shown by the Biuret test. Bacterial action was more pronounced than enzyme action, in fact, the enzyme had lost most of its activity. The foregoing process was repeated on liquefied egg white in a neutral medium rather than in a tenth normal alkaline medium, without obtaining better results, that is, the egg was no more changed than it was when digested in the alkaline medium.

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\* From the Medical Clinic of the Peter Bent Brigham Hospital. The expense of this investigation was defrayed by the Surdna Foundation of New York.

## SUMMARY

Just as on percussing the air-containing lung, the specific sounds of the two mutually dependent and connected systems—chest wall and lung—determine the percussion sound, so the breath sound over the air-containing lung is composed of two specific sounds that of the bronchial system and that of the air-containing lung tissue

Only the sound of the chest wall is heard on percussion over a massively infiltrated lung, the lung itself remains mute. The specific sound of the infiltrated tissue has no part in bronchial breathing obtained over an infiltrated lung. Pathologic bronchial breathing is merely the expression of correctly transmitted vibrations

During respiration the air in the bronchi is caused to vibrate in the form of split and cut sounds. The glottis is not necessary for this purpose

The graphic registration of the "lung traveling voice" shows the great importance of the laws of the so-called forced vibrations in the problem of auscultation

The intestine extract was prepared from fresh pig in the following manner. Twenty-five feet of intestines beginning at the pylorus were washed by running cold water through, then the intestine was chopped finely and allowed to soak over night in 250 c c of twentieth normal hydrochloric acid which contained 1 per cent of glycerin. The following day the mixture was strained through cheese cloth, then through cotton and preserved by the addition of 1 c c of a 5 per cent alcoholic thymol solution and kept on ice.

*Digestion of Egg White*—The whites of a dozen hard boiled eggs were pressed through a potato ricer and placed in a 2 liter flask with 1,500 c c of 0.1 per cent hydrochloric acid, and a small amount (usually 4 c c) of alcoholic thymol (5 gm thymol dissolved in 100 c c of 95 per cent alcohol) was added to prevent bacterial growth. To the contents of the flask were added 75 c c of fresh pig stomach extract and incubated over night in a water bath at 40 C. Then 75 c c more of pig stomach extract were added and incubated another twenty-four hours. At the end of this forty-eight hours' digestion, 300 c c were removed and called fraction No. 1. The remaining contents of the flask from which No. 1 was withdrawn were made slightly alkaline (refer Table 1) to litmus by the addition of a saturated solution of sodium carbonate. Then 25 c c of pancreas extract and 20 c c of intestine extract were added. Incubation was continued for forty-eight hours at 40 C, at the end of which time 200 c c were removed and called fraction No. 2. From now on the process remained the same, namely, at the end of each forty-eight hours of incubation a fraction was withdrawn until a total of five or six fractions were obtained. After withdrawal of each fraction, 25 c c of pancreas extract and 20 c c of intestine extract were added. Throughout the digestion, after fraction No. 1 had been withdrawn the contents were kept alkaline by the addition of a little sodium carbonate, but not more alkaline than 0.1 normal. Thymol was present throughout to prevent bacterial growth.

A similar experiment was carried on without thymol, thus allowing bacterial growth to take place, with the result that digestion proceeded much more rapidly, and the amino acid stage was reached much more rapidly. Since the bacterial action would complicate the enzyme and foreign substances other than those due to simple enzyme activity would be formed, thymol was added as noted above.

*Digestion of Beef, Pork and Lamb*—One and one half pounds (680 gm) of finely chopped lean meat were placed in a 2 liter flask with 1,500 c c water and sterilized in the autoclave at 15 pounds' (7 kg) pressure for twenty minutes. The mixture was then cooled to 100m temperature, made slightly acid to litmus with hydrochloric acid, and the same process as described for egg white was then carried out, except that only 2 c c of thymol solution were added.

Since it was thought probable that natural digestion was carried on with a greater dilution of protein than that we had used (our egg being very concentrated), we tried a dilute solution of peptonized egg white. After three days of incubation with 150 c c of duodenal contents, the biuret reaction showed a light pink, showing that digestion had progressed further than it had with the concentrated egg white. A biuret-free stage, however, could not be reached without having present a considerable amount of bacteria which were probably due to contamination of the duodenal contents, since the liquefied egg and containers had been sterilized.

By further experimentation, we found that duodenal contents would completely digest a weak solution of protein, provided the duodenal contents contained sufficient natural buffer. We did not know, however, how much of the digestion was due to bacteria and how much was due to enzyme activity.

Therefore, since too dilute a solution of protein had to be used in the digestion by human duodenal contents, and furthermore since the duodenal contents contained bacteria which probably are not present in a person and which played some part in digestion although we could not tell of how much import they were, another method of digesting proteins was employed—artificial digestion.

#### ARTIFICIAL DIGESTION

The common food proteins, namely, egg, wheat globulin, milk, beef, lamb and pork, which often cause asthma, eczema and perennial hay-fever, and to which such patients are sensitized, were selected for the digestion experiments. These proteins were digested in the following manner:

*Extraction of Enzymes from Fresh Glands*—The fresh pig stomach extract referred to in the digestion of the proteins was obtained as follows. The glands were removed from the wall of fresh pig's stomach, washed in cold water for a few minutes, cut up finely and allowed to soak over night in twentieth normal hydrochloric acid containing 1 per cent of glycerin, 250 c c of acidulated glycerin solution were used for each stomach gland. The mixture was strained through cheese cloth and then through cotton, the filtrate should be almost clear. The filtrate which contained the enzyme pepsin was preserved with 1 c c of a 5 per cent alcoholic thymol solution and kept in the icebox.

The pancreas extract was obtained by chopping finely fresh pig pancreas and allowing it to stand over night in 200 c c of one hundredth normal hydrochloric acid, to which was added 1 c c of glycerin. The following day the mixture was strained through cheese cloth and then through cotton. The extract was preserved by addition of 1 c c of a 5 per cent alcoholic thymol solution and kept on ice.

The casein used in the table was a solution of 1 gm casein in 100 c c water and 4 c c tenth normal sodium hydroxid. The enzyme used consisted of 1 c c of pancreas extract (already described) and 1 c c intestine extract (already described), diluted with water. Two c c of a 25 per cent metaphosphoric acid solution was used to precipitate the protein. The various tubes containing the ingredients as per table were incubated 30 minutes at 40 C.

The foregoing experiment definitely shows that trypsin has five times more proteolytic activity in a one fifteenth molecular alkaline phosphate solution than it has in a one fifteenth molecular acid phosphate solution. For this reason, in the digestive experiments, the acid reaction after pepsin digestion was changed to an alkaline reaction before the addition of trypsin.

#### SENSITIZATION TESTS WITH THE DIGESTIVE FRACTIONS

It seemed desirable first to test the digestive fractions on a group of patients who gave positive cutaneous tests with the whole protein,

TABLE 1—*The Effect of Acid and Alkaline Phosphate on Trypsin*

Tube	Casein	1/15 Molecule Sodium Phosphate	1/15 Molecule Potassium Dihydrogen Phosphate	Dilute Enzyme Solution	Mg Nitrogen per 100 C c of Filtrate
I	5 c c	0 c c	5 c c	1 c c	0.4
II	5 c c	1 c c	4 c c	1 c c	0.55
III	5 c c	2 c c	3 c c	1 c c	1.40
IV	5 c c	3 c c	2 c c	1 c c	2.00
V	5 c c	4 c c	1 c c	1 c c	3.50
VI	5 c c	5 c c	0 c c	1 c c	5.00

in other words, to test known sensitive patients with the digestive fractions. In Table 2 are presented the results of the cutaneous test with both the whole protein and its digestive fractions. For convenience the table is divided into Part A and Part B. The first column of each part shows the patient's diagnosis, the second column contains the patient's initials, the third column shows the particular protein to which the patient is sensitive and also the size of the cutaneous reaction or the degree of sensitiveness of the patient to that protein, for instance, a plus means a wheal at least 0.5 cm in diameter, a 1+ means a little larger reaction, a 2+ means a wheal at least 1 cm in diameter, and so on. The columns headed *digestive fractions* gives the results with each fraction of the protein to which the patient is sensitive, a  $\pm$  means a doubtful reaction, 1— means a more definite reaction than  $\pm$  but not enough to call a + and a question mark means that there was a slight reddening or irritation which should probably be called negative. In fact, probably all reactions labeled  $\pm$  or question mark should be called



*Digestion of Milk*—In a 2 liter flask were placed 1,500 c c of skimmed milk, to which were added 1 c c of hydrochloric acid and 2 c c of thymol. From now on the process was identical with that described for egg white.

*Preparation and Digestion of Wheat Globulin*—Whole wheat flour (300 gm) was placed in a large container and extracted twice with 4 liters of 10 per cent sodium chlorid. The mixture was stirred until the flour and salt were thoroughly mixed and is allowed to stand three days. In a similar manner the wheat flour was extracted a second time with 4 liters of 10 per cent sodium chlorid, thoroughly mixed and allowed to stand three days. The flour settled to the bottom and the pinkish supernatant fluid was siphoned off. From the supernatant fluid obtained from both extractions together, the globulin was precipitated by saturation with sodium chlorid. The precipitated globulin settled to the bottom after several days so that the supernatant fluid could be decanted and the contents at the bottom of the flask centrifuged at high speed, thus separating out the globulin. The globulin was then placed in a 2 liter flask to which 1,500 c c of water were added and sufficient hydrochloric acid to make the mixture slightly acid to litmus. Three cubic centimeters of thymol solution were added, and from then on the process was the same as described for egg white.

#### FURTHER TREATMENT OF DIGESTIVE FRACTIONS

The various fractions of digestion were treated as follows. In order to have them in a dry powdered form, each fraction was evaporated slowly on a water bath until an almost dry, sticky residue was obtained. Then 50 c c of 95 per cent alcohol were added and thoroughly mixed with the sticky residue and again evaporated. This process was repeated four times to remove water. The residue was finally dried in a vacuum desiccator containing sulphuric acid and powdered with a mortar and pestle. The powder is very hygroscopic and needs to be kept in air tight bottles. With wheat globulin the fractions were evaporated to dryness on a water bath placed in front of an electric fan which kept the air over the evaporating dish in circulation. To the dry residue, 100 c c of absolute alcohol were added, and the mixture was allowed to stand at room temperature for thirty minutes. Then the mixture was stirred, filtered, pressed through a filter paper to express as much alcohol as possible and finally dried in a sulphuric acid vacuum desiccator. When dry the substance may be powdered as was done with the other digestive fractions, as already described. With the wheat globulin digestion was carried through five fractions rather than six as was the case with the other food proteins.

Table 1 shows why, after pepsin digestion, the mixture was made alkaline before the addition of trypsin.

protein, and in only five instances were the tests with the first two fractions as positive as with the whole protein. In the majority of cases, there was a decrease in the positiveness of the reaction as the succeeding fractions were tested. In cases C P with egg, A C C with lamb, A J A with pork, and P K with beef, the fifth and sixth fraction did react more strongly than the other fractions, but these reactions were less marked than the reactions given by the whole undigested proteins, with only one of these four patients (P K) was the reaction given by the fifth or sixth fraction a real positive, and with this case the sixth fraction was negative. Therefore when digestion was most complete and the greatest quantity of amino acids were present in the substance being tested, an occasional weakly positive reaction was given but such reaction was in no instance as large as that given by the undigested protein. From this part of the table it might be concluded that the digestive products of protein probably do not sensitize, or at least when the whole or undigested protein does give a definite positive reaction, its digestive products give less positive reactions, and the more complete the digestion is the less is the reaction given.

In Part B of Table 2 are represented three patients who had eczema, one who had angioneurotic edema, ten who had bronchial asthma and the fifteenth or last patient who had gastro-intestinal cramps and colic. In only three instances did the first fraction of digestion give any reaction, and in only one (P K) was the reaction definitely positive. These three reactions might well be due to the presence of undigested protein. In no instances did the other fractions of digestion give any reaction. Therefore this part of the table furnishes strong evidence against sensitization to the digestion products of proteins in those patients who are definitely sensitive to the whole protein.

Since known positive food cases, as shown in this table failed to give positive reactions with the digested products, it would not be expected that patients who failed to be sensitive to the whole protein would be sensitive to the digestive products. A large number of patients who had bronchial asthma and eczema, and who failed to give a positive cutaneous test with whole proteins, were tested with these digestive fractions, and in only two instances were reactions obtained. One, a patient with eczema that reacted slightly to casein, did react more positively to fractions one and two of milk, but failed to react to the other fractions. The other patient also had eczema and did react positively to the first four fractions of wheat globulin, whereas whole wheat globulin and fraction five failed to react. These two cases, however, considering the large number tested, do not change the conclusions already stated, namely, that the digestive products of proteins probably do not sensitize.

negative, and those designated 1— probably mean nothing when compared with such definite reactions as were given by the whole protein

The first five patients in Part A of Table 2 had eczema, the sixth had angioneurotic edema and the remaining twelve had bronchial asthma. It is noted that the majority of the patients reacted positively with the first fraction of digestion, and nearly all of these same patients

TABLE 2—Results of Cutaneous Tests with Whole Protein and Its Digestive Fractions

Diagnosis	Patient	Protein	Digestive Fractions					
			1	2	3	4	5	6
Part A								
Eczema	F H	Globulin	+	+	+	+	+	+
Eczema		Egg	1+	?	?	?	?	?
Eczema	G H W	Globulin	+	+	+	+	+	+
Eczema	C P	Globulin	+	1—	+	+	+	+
		Egg	+	?	?	?	?	1—
Eczema	F D	Milk	2+	+	0	0	0	0
Angioneurotic edema	F	Globulin	1+	+	?	?	?	?
Asthma	W J D	Globulin	+	1+	1—	1+	?	?
Asthma	A C C	Pork	+	1—	+	0	0	0
		Lamb	+	0	?	?	1—	1—
Asthma	J F P	Globulin	3+	1+	+	1—	1—	1—
Asthma	M L B	Globulin	1+	1+	+	+	+	+
Asthma	C G F	Globulin	2+	+	+	+	+	+
Asthma	A J A	Pork	1+	0	0	+	+	1—
Asthma	P K	Beef	1+	+	1—	+	+	?
Asthma	F R	Globulin	+	+	+	+	?	?
Asthma	J L	Globulin	+	+	+	0	0	0
Asthma	J M	Globulin	2+	2+	+	+	+	+
Asthma	W T M	Globulin	1+	1—	1—	+	+	+
Asthma	Bar	Globulin	1+	+	+	0	0	0
Part B								
Eczema	R J	Casein	+	0	0	0	0	0
Eczema	G H W	Egg	+	0	0	0	0	0
		Milk	+	0	0	0	0	0
Eczema	F D	Egg	2+	0	0	0	0	0
Angioneurotic edema	F	Beef	+	0	0	0	0	0
Asthma	A C C	Beef	+	0	0	0	0	0
Asthma	J R	Globulin	2+	0	0	0	0	0
Asthma	A O F	Egg	1+	0	0	0	0	0
Asthma	C A N	Pork	+	0	0	0	0	0
		Lamb	+	0	0	0	0	0
Asthma	P H F	Pork	1+	+	0	0	0	0
Asthma	F S	Globulin	1+	0	?	0	0	0
Asthma	E McC	Egg	1+	?	?	?	?	?
Asthma	L S	Globulin	+	?	?	?	?	?
		Egg	+	+	0	0	0	0
Asthma	P K	Egg	+	0	0	0	0	0
		Globulin	+	+	0	0	0	0
Asthma	H F B	Pork	+	1—	0	0	?	?
G I	Dr B	Pork	+	0	0	0	0	0

reacted positively to the second fraction, but in only five instances did the third fraction give a positive reaction, the fourth fraction gave positive reactions in only three instances, and the fifth fraction in four instances, the sixth fraction gave a weak test in three of the seven cases tested. In other words, the first two fractions reacted more nearly like the whole undigested protein, and their positive reactions might well be explained as being due to the presence of the original protein which had not yet been acted on by digestion, in no instance did the first two fractions react more strongly than the original whole

that the delivery tube (one side arm) was at an angle of 45 degrees, and it was inserted into the neck of another or receiving flask which was held at the proper angle by means of a clamp. The other or free side arm was used for applying the vacuum. A manometer placed in the vacuum line helped to control the temperature by applying approximately the same degree of vacuum from day to day, a vacuum of 480 mm of mercury was used.

In a similar manner wheat globulin, milk and beef were treated, and from each five fractions were obtained for use in testing patients.

A series of twenty-five patients who were sensitive to one or more of the whole proteins were tested with all of the bacterial fractions obtained from each protein. A table illustrative of these tests would be too long and too complex to be of any advantage, therefore a general summary of such a table is given. About one third of the patients failed to give a positive reaction with any of the fractions and another third gave positive reactions with most of the fractions. However, as many patients who were negative to the whole protein gave a positive reaction with its fractions as did those who gave positive reactions with the whole protein. In other words, the fractions gave positive reactions irrespective of whether the whole protein did or did not react positively. In the remaining third of the series, some of the fractions reacted positively, but the majority of the fractions failed to react, more often, those who would be expected to react positively failed to do so, and vice versa. The fractions obtained from the digestion of all proteins with *Bacillus coli-communis* gave the largest number of positive reactions, and the fractions obtained from the digestion of all four proteins by *Bacillus acidophylus* gave the smallest number of positive reactions. These results could not be correlated with the positive tests with the whole protein. Furthermore, in no instance was a two plus reaction obtained, and often a doubtful or  $\pm$  reaction was given. From these varying and erratic results, we felt that we were getting no true anaphylactic reactions, but instead that the fractions were irritative to the skin and nonspecific reactions were being obtained due to irritation of the fractions.

In order to determine whether the fractions were irritative to the skin or not, thereby giving false reactions, a series of twenty-five patients who had various conditions and whom we had no reason to believe were sensitive to proteins and in whom the whole protein gave negative reactions, were tested with all of the fractions obtained from the four proteins that were digested with the bacteria. In other words, the foregoing experiment was duplicated, using known negative cases. In this series of cases, one third gave negative reactions with all of the fractions of all four proteins. Four other cases gave positive reactions with beef digested with *Bacilli coli-communis* alone but were negative to all of the other fractions of beef as well as to milk, globulin and

## ARTIFICIAL DIGESTION WITH BACTERIA

As already stated, the previous digestion experiments were carried on under sterile conditions. Since in the human intestinal tract bacteria are normally present, we allowed bacteria to digest or act on the proteins. As bacteria probably play little or no part in digestion of proteins in the stomach, duodenum and upper intestinal tract, we digested the proteins as previously described up to and including the point where the second fraction was removed, in other words, we allowed the proteins to be acted on by pig stomach extract in the presence of hydrochloric acid for forty-eight hours, then neutralized and allowed pig's pancreas and intestine to act on the proteins for forty-eight hours. The mixture was then sterilized at 15 pounds' pressure for twenty minutes in order to kill the enzymes and stop their activity. This partially digested protein mixture, as shown by the fact that the biuret test showed no true protein to be present, was equally divided into three parts, and each part was placed into a sterile flask. To the contents in each flask were added 2 gm of lactose and 3 cc of glycerin in order to give the bacteria about to be added a more nutrient medium until they might become adapted to growth in the protein digestion mixture. We selected *Bacillus acidophilus*, *Bacillus coli-communis* and *Bacillus proteus* for continuing the digestion, because the former is a normal inhabitant of the infant's gastro-intestinal tract, and in the adult its administration seems to be efficacious in the relief of some conditions, more especially in the relief of obstinate diarrhea and digestive disorders. The latter two organisms are normal inhabitants of the gastro-intestinal tract of older persons, and in addition *Bacillus coli-communis* does decompose proteins, or is proteolytic.

One flask was inoculated with each of the foregoing organisms and incubated for four days at 37 C. At the end of this time, the contents of each flask were examined to make sure that the bacteria were still alive. One hundred cc were withdrawn from each flask, sterilized and evaporated to 8 cc under vacuum at a temperature not above 50 C. These samples were called fraction No 1. The remaining contents of each flask were incubated another period of forty-eight hours, after which the contents were examined to demonstrate that the bacteria were still living, then another 100 cc were withdrawn and sterilized and evaporated as before. This was called fraction No 2. In a similar manner, fractions No 3, No 4 and No 5 were obtained.

All fractions were then heated for one hour at 65 C, after which they were transferred to sterile bottles and kept on ice for future use in testing patients.

The evaporation of each 100 cc withdrawn was carried out in the following manner. Into flasks with two side arms were placed the 100 cc of digestion mixture, the flask was suspended in a water bath so

or diminished to any appreciable extent the irritability of the fractions. For these reasons further experimentation with these bacterial fractions was discontinued.

Although further consideration of the bacterial digestive products seemed to be unwarranted, the testing of eczema patients with the sterile fraction was continued until a series of fifty persons was completed. The results verified the conclusions already stated. Therefore, contrary to our expectations, eczema patients are not sensitive to the decomposition products of proteins, and we have no evidence that the partially or completely digested protein causes eczema. When proteins cause eczema, as they often do, the whole or undigested protein is the causative agent.

#### SUMMARY

We attempted to digest proteins with normal human duodenal contents but failed because the action of the bacteria which was present in the duodenal contents was more pronounced than the activity of the enzymes, furthermore, too dilute a solution of protein had to be used to make the results practical.

Artificial sterile digestion using pig's stomach, pig's pancreas and pig's intestine extracts was successful. Since egg white, beef, pork, lamb, milk and wheat globulin are the usual proteins to which patients with asthma and eczema are sensitive, these proteins were selected for digestion. Every forty-eight hours a fraction of digestion was removed, namely, fraction No. 1 after forty-eight hours in the presence of stomach extract and hydrochloric acid, fraction No. 2 after forty-eight hours in the presence of pancreas and intestine extracts in an alkaline medium, and fraction Nos. 3, 4, 5 and 6 each after forty-eight hours' successive intervals. The proteins soon lost their identity as such, and the amino acid stage was gradually reached until in the last two fractions only amino acids were present. The various fractions were treated until a dry, hygroscopic powder was obtained, and with these cutaneous tests were made.

In Table 2 are presented the results of tests with these fractions on known sensitive patients. The first two fractions reacted positively in a number of cases, but it is not certain that sufficient undigested protein was present to account for these positive tests. The later fractions usually reacted only slightly positively or not at all. This table would seem to show that digestive products do not sensitize, even though the whole protein from which the fraction was derived does react positively. A series of patients who failed to react positively to the whole protein reacted likewise negatively to the digestive products.

Artificial digestion was then carried out in the presence of bacteria as follows. After digestion through the second fraction was completed, the mixtures were sterilized, divided into three parts and to each portion was added respectively, *Bacillus coli-communis*, *Bacillus proteus*

egg Three other patients gave positive reactions with beef and milk coli communis fractions but negative reactions with all other fractions The remaining cases reacted too irregularly to warrant description The beef and milk *Bacilli coli-communis* fractions reacted most frequently and all *Bacillus acidophilus* fractions reacted least often (in only five patients did these fractions give any reaction) No patient reacted to every fraction, in only three instances was a two plus reaction obtained, and frequently a doubtful or  $\pm$  reaction was given This experiment duplicated closely the former one, therefore similar erratic results were obtained with both known sensitive and known nonsensitive patients It would therefore seem that the fractions were irritating to the skin and that some fractions were more frequently irritating than others

Although a definite interpretation cannot be made from the results of the two foregoing experiments, we can definitely state that the evidence is against sensitization of persons to the digestion products of proteins obtained through the action of the usual intestinal bacteria

The suspected irritative property of the bacterial fractions we attempted to remove by dialysis, since some fractions were very acid and others very alkaline, it was possible that the increased acidity or alkalinity might be the source of irritation, furthermore the black coloring matter present in the fraction might be irritable All fractions were dialyzed until they were practically neutral, and all coloring matter in the majority of the fractions had disappeared

Twenty-five patients with miscellaneous conditions were tested with the dialyzed fractions, with the following results Only one patient gave negative reactions with all of the fractions, whereas previous to dialysis eight patients reacted negatively Three other patients gave only doubtful tests with the fractions of one protein, and no patient reacted to all of the fractions of all proteins No positive reactions were given by the fractions of egg digested by *Bacillus acidophilus* or by *Bacillus proteus*, and only one patient gave positive reactions with egg digested by *Bacillus coli-communis*, therefore dialysis did diminish the number of positive reactions obtained by egg bacterial digestion With milk, however, a larger number of positive reactions were obtained after dialysis than was the case before dialysis, and with the globulin fraction the results were practically the same both before and after dialysis With beef *Bacillus acidophilus* and *Bacillus proteus* fractions gave similar results both before and after dialysis, whereas *Bacillus coli-communis* fractions gave six less positive reactions after dialysis than they did before dialysis but even here the fifteen positive reactions were far too many for supposedly negative patients In general, dialysis seemed to render some fractions more irritable, other fractions less irritable and the remaining fractions remained unchanged Therefore, neither the removal of coloring matter nor the change in reaction, either acid or alkaline to neutrality, lessened our difficulty of false reactions

# THE VITAL CAPACITY OF THE CHINESE AN OCCUPATIONAL STUDY ~

JOHN H FOSTER, MD

AND

P L HSIEH, MD

CHANGSHA, CHINA

The use of the spirometer as a clinical instrument of precision, introduced by Jonathan Hutchinson in 1846, has been brought into more general use through the more recent researches of Peabody,<sup>1</sup> Wentworth,<sup>2</sup> Dreyer,<sup>3</sup> West,<sup>4</sup> Wilson, Edwards,<sup>5</sup> Lundsgaard, Van Slyke,<sup>6</sup> Hewlett and Jackson<sup>7</sup> and others. The normal standards suggested by Hutchinson have been modified, and the relation to the body measurements of height, weight, body surface, chest volume and circumference have been determined for various groups of persons.

The value of spirometry as an index to the patient's clinical condition has already been demonstrated in cardiac<sup>8</sup> and pulmonary disease.<sup>9</sup> Conditions necessary for the more general adoption of this method are (1) a simple technic, (2) accurate normal standards with knowledge of the normal range, and (3) knowledge of the factors influencing vital capacity. The first is fairly standardized, and although the apparatus is cumbersome and not easily portable, it is easy to manipulate and accurate, provided the cooperation of the patient can be obtained. Normal standards for men, women and children have been investigated, and figures representing the ratios of vital capacity to body surface

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\*From the Department of Medicine, Hunan-Yale College of Medicine

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and *Bacillus acodophilus* After the addition of these bacteria, fractions were withdrawn each forty-eight hours until a total of five fractions were obtained, and with these the patients were tested

In a series of known negative miscellaneous cases, these bacterial fractions gave too numerous and too erratic results, which were attributed to the possibility that the fractions were very irritable to the skin Since some of the fractions were quite acid and others were quite alkaline and all contained a dark coloring matter, the fractions were dialyzed until all were approximately neutral and practically free from coloring matter The dialyzing, however, seemed to make little difference in the results of tests on known negative patients, therefore further experimentation with the bacterial fractions was discontinued

A series of patients with eczema were then tested with the dry fractions obtained by sterile digestion, with the result that the patients who failed to give positive tests with the whole protein likewise gave negative tests with their digestive products Therefore this work would seem to show that there was no advantage in testing patients with the digestive fractions of proteins and that probably digestive products do not sensitize

#### CONCLUSIONS

When whole proteins give a strong reaction, the amino acid of the corresponding protein does not The suspected substance which might react on the anaphylactic patients was thought to lie somewhere between the true proteins and the amino acids, but the results obtained in this work tend to show that the further one gets away from the true protein the less the reaction This is borne out clinically by the fact that the known protein anaphylactic cases react quickly after the ingestion of the protein, to which they are sensitive

It seems reasonable to assume that anaphylaxis does not take place until the offending protein gets into the blood, therefore, there must be a slight assimilation of an almost true protein or slightly altered protein which, considering the short space of time between the ingestion of the protein and the anaphylactic reaction, could be no more than peptonized

Peptones and proteoses prepared by the simple hydrolysis of proteins may cause sensitization as has already been shown<sup>1</sup>

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<sup>1</sup> Wodehouse, R P Immunochemical Studies of the Plant Proteins Proteins of the Wheat Seed and Other Cereals Study IX, *Am J Botany* **4** 417, 1917 Walker, I C Studies on the Sensitization of Patients with Bronchial Asthma to the Different Proteins Found in the Dander of the Horse and in the Hair of the Cat and the Dog and to the Sera of These Animals, *J Med Res* **35** 497, 1917 Wodehouse, R P Immunochemical Studies of the Proteins of Cat Hair Study VI, *Immunochemistry of the Proteins of Horse Dander*, Study VII, *Immunochemistry of the Proteins of Dog Hair*, Study VIII, *J of Immunol* **2** 227, 234 and 237 1917 Walker, I C The Treatment of Patients with Bronchial Asthma with Subcutaneous Injections of the Proteins to Which They are Sensitive, *J Med Res* **36** 423, 1917

were not accepted. All were doing their daily work and were in apparent good health. Weights were taken in pounds on the hospital balance scales and on a portable spring scale which had been checked with the balance type, and later changed to kilograms. Measurements were taken with clothing on. As the amount of clothing varies considerably in different classes of persons and in different seasons of the year, an average costume for each group was weighed and correction was made at the time of calculation. As some were barefoot, a correction was made for those wearing shoes. Body surface was determined from the height and weight by use of the DuBois<sup>12</sup> chart. Ratios to body surface and to height were calculated and the results tabulated.

#### RESULTS OF INVESTIGATION

Records of over 600 were obtained, representing many types, ages and occupations, of these, only 500, in ten groups, were taken for analysis. The results can be best appreciated by a brief discussion of each group.

*Soldier Group*—In this group were ninety-seven soldiers, 18 to 40 years of age, from the Changsha military barracks. They probably represent the average soldier of the Hunan provincial troops. Records were taken after a daily drill. Deductions of 4 pounds (2 kg) for weight of uniform and 1 cm for height were made. The average for the group was 1.89 for surface and 1.88 for height ratio, the figures ranged from 2.57 to 1.34 and from 26.1 to 13, respectively.

*Policeman Group*—This group included forty members of the Changsha civil police force and represents the average young adult male of Changsha engaged in a moderately active outdoor occupation. The same correction for uniform and shoes was made as for the soldiers. The averages here were slightly higher, being 2.09 for surface and 1.97 for height, the extremes ran from 2.82 to 1.45 for the former and from 27.4 to 13 for the latter.

*Workman Group*—This group included forty-nine artisans from different trades, including carpenters, masons, painters, weavers, printers, shoe-makers and barbers. This is more of a social classification than a similar type of labor. Hours of work are long, from twelve to sixteen hours a day. The ages run from 17 to 40. Three pounds (1.4 kg) were deducted for weight of clothes and 8 cm for height of shoes. An average of 2.03 for surface and 1.95 for height was obtained, the upper and lower limits being 2.69 and 1.37 for surface ratio and 26.1 and 12.8 for height.

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<sup>12</sup> DuBois, D.; and Dubois, E. F. Clinical Calorimetry. Tenth paper. A formula to Estimate the Approximate Surface Area if Height and Weight be Known, Arch Int Med **17** 863 (June) 1916.

and to height, in terms of liters per square meter of surface and in cubic centimeters per centimeter of height, have been adopted West,<sup>4</sup> after an analysis of eighty-five medical students and forty-four nurses, decided on 2.5 liters per square meter body surface for men and 2 liters for women as a normal. A ratio of 25 c.c. per centimeter of height for men and 20 c.c. for women was also proposed, men with an athletic history were given 28 and 29 as surface and height ratios, respectively. Wilson and Edwards,<sup>5</sup> from a study of 362 school children in New York City, adopted standards for children of 1.93 for surface and 15.5 for height ratios.

Clinical studies and reports are leading to a clearer understanding of the importance of the various factors which affect vital capacity, such as diseases of the heart and lungs, general physical condition, body strength and weakness,<sup>10</sup> and the effect of age, race, athletics, posture,<sup>11</sup> social environment, etc. All are necessary for a proper evaluation of results.

#### METHOD

In taking vital capacity measurements on Chinese during routine physical examination of students of the College of Yale in China and city schools, also of patients in the Hunan-Yale Hospital, it was found that the vital capacity of the Chinese fell considerably below the standards adopted for Americans. The following investigation was therefore undertaken to determine a normal standard for the Chinese, and incidentally, to study the effect of various occupations on the vital capacity.

The instrument used was a water spirometer of 6½ liters' capacity. This was copied by a local brass smith from a Narragansett Machine Company model owned by the local Y. M. C. A. Our machine was calibrated by the physics department of the premedical department, and, in operation, has checked accurately with the original.

The procedure in each case involved a careful explanation and demonstration of the method. Care was taken to see that the person took his deepest inspiration. Maximum efforts were stimulated by the competition which always developed when a number were being tested. Two to five attempts were recorded, and the highest taken as the vital capacity. Unsatisfactory cases were discarded. Routine physical examinations were not attempted, although men with gross defects

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<sup>10</sup> Peabody, F. W., and Sturgis, C. C. Clinical Studies of the Respiration VII. The Effect of General Weakness and Fatigue on the Vital Capacity of the Lungs, *Arch. Int. Med.* **28**: 501 (Nov.) 1921.

<sup>11</sup> Christie, C. D., and Argyll, J. B. The Estimation of Normal Vital Capacity with Especial Reference to the Effect of Posture, *Arch. Int. Med.* **30**: 34 (July) 1922.

2 pounds were deducted from the weight. The surface ratio for this group was 2.13, for height, 20.3. The extremes were 2.52 and 1.5 for the former, 25.2 and 14 for the latter.

*Students' Group*—There were thirty-six in this group, including medical students, hospital interns and a few male nurses. The ages ranged from 19 to 31. These represent a rather picked group of normal active young adults, although they are more athletic than the ordinary Chinese. A correction of 4 pounds was made for clothes and 1 cm. for shoes. The averages for this group were 2.18 surface and 21 height ratio, the figures ranged from 2.56 to 1.74 for the former and 25.6 to 16.4 for the latter.

*Female Students*—In this group were seventy-five girls, from 16 to 22 years of age, from the Fu Siang Girls' School and from the Hunan-Yale School of Nursing. All had had physical examinations before these records were taken. The group represents the average well-developed Chinese young woman. The height and weight figures show what small bodies most of the girls have. No correction was made for clothing. The averages here were 1.54 for surface and 14.3 for height ratio, with the extremes of 2.08 and 0.99 for the former, 19.4 and 9.2 for the latter.

*Foreigners' Group*—The records of twenty-five occidentals were obtained for comparison with the Chinese. In this group were included physicians of the hospital staff, teachers in the College of Yale in China, local business men and some sailors from the U. S. S. *Quiros*. The ages ranged from 19 to 48. No deductions were made for clothing, so the results are slightly lower than if measurements were taken stripped. The averages for the group were 2.39 liters per square meter of body surface and 25.1 c.c. per cubic millimeter of height. The extremes here were 2.87 and 1.64 for surface, with 31.8 and 18.9 for height ratios.

#### COMMENT

A study of the vital capacity of 425 men and seventy-five women in different groups of Chinese (Table 1) shows a general average of 2.02 liters per square meter of body surface for the men and 1.53 for the women. For convenience, the flat figures of 2 and 1.5 have been adopted as the normal standard for surface ratio for men and women, respectively. An analysis of the individual cases according to occupational groups (Table 2), shows only 42 per cent of the men and 51 per cent of the women within plus or minus 10 per cent of the standard, about 20 per cent of both men and women are below 90 per cent. Compared with the American standard of 2.5 for men and 2 for women, we find that 80 per cent of the men and 85 per cent of the women fall below 90 per cent of the normal.

*Shop Clerks*—Forty men were obtained from one of the silk stores in the city. They represent a fairly well-to-do class in a sedentary occupation. Records were taken in the shop at the end of the day's work. Three pounds (1.4 kg) were deducted for clothes and 1 cm for shoes. These men are the smallest in size and have the lowest ratios of any group of men except the soldiers, being 1.90 liters per square meter of body surface and 17.6 cc per centimeter of height. The extremes were 2.39 and 1.13 for surface and 21.9 and 10.2 for height.

*House Coolie Group*—Altogether, forty-nine subjects of this group were studied. They were the indoor coolies<sup>13</sup> of the Hunan-Yale Hospital and Changsha Y. M. C. A. Their hours of work are long, but the work is not arduous, being mostly that of the janitor, housemaid, orderly, doorkeeper, watchman, or messenger type, etc. Four pounds (2 kg) were deducted from the weight and 1 cm from the height. Figures for this group were 2.12 surface ratio and 20.5 for height, the maximum being 2.68 and 25.5, the minimum 1.79 and 17.1, respectively.

*Ricksha Coolie Group*—These men put in long hours pulling, generally on the run, the two wheeled passenger jinrickshas. This is the common method of travel in the large cities, and one would expect the coolies to develop extraordinary powers of endurance and wind, as the work is quite exhausting. In Changsha the rough streets do not permit great speed, so the work is a little harder than the ordinary coolie labor. Forty men were studied. The ages ranged from 20 to 50. All were barefoot, only 2 pounds (1 kg) were subtracted for clothes. The average for this group was 2.01 for surface ratio and 19.3 for height, the upper and lower limits being 2.5 and 1.5 for surface, 23.5 and 14 for height. It is likely that in Shanghai, Hankow, Peking, or other better paved cities, the figures for this group would differ.

*Carrying Coolie Group*—Forty of this type of laborer were obtained in two of the coolie guilds in the city. These men carry heavy burdens suspended from a pole which is carried on the shoulder. A large part of the freight in China is handled in this manner. It is heavy work and the men are noted for their endurance. They represent a group of strong and muscularly developed workers. They were barefoot, 2 pounds were deducted for clothes. The results for this group were 2.01 for surface and 19.7 for height ratios, the figures ranging from 2.54 to 1.65 and from 26.5 to 15.7, respectively.

*Glassblowers' Group*—In this group also forty were studied. They were found in two glass factories in the city. This is a hard working group, blowing glass puts a great strain on the expiratory muscles, and one would expect an increase in lung capacity. They were barefoot,

13 "Coolie" is the Eastern term for the common laborer.

Height ratios show an average of 19.5 c.c. per centimeter of body height for men and 14.3 for women. The flat figures of 19 and 14 were taken as the normal standard. A study of the individual and group variations (Table 3) shows a general similarity to the body surface ratios, only 50 per cent of the men and 48 per cent of the women are within 10 per cent of standard, with approximately the same proportion as above falling below 90 per cent. The height ratios seem to show a wider range, yet, on the whole, follow the surface ratios closely. Compare these results with the Western standards of 25 c.c. per centimeter of height for men and 20 for women, and we find that only fifty-one men and five women are within 90 per cent of those figures, that is, 88 per cent of the men and 93 per cent of the women are below 90 per cent.

A comparison of the averages of the occupational groups shows some differences which seem to be greater than the normal error. The soldiers have the lowest vital capacity with an average surface ratio of 0.13 below the general average, while the students are the highest with 0.16 above. The reason for the low figures for this group of soldiers is not apparent, although one is tempted to question their physical fitness. The shop clerks, with little physical work, have a low lung capacity, almost as low as that of the soldiers. The coolies of different types have about the same ratios. It is surprising that the ricksha coolies have not a higher vital capacity, their capacity being lower than that of the house coolies whose work is chiefly indoors. The glass blowers, as expected, have the highest capacity of all the laborers, although theirs is lower than that of the students. The students, on the whole, had been fairly active in sports, basket ball and soccer football, and it would seem as though athletics were the important factor in this case. This seems to confirm the doubt raised by Hewlett and Jackson that standards based on a picked group, such as college students, are too high for the general public.

The average for women is much lower than for men. This is in keeping with the difference noted by West, and the proportion is approximately the same. It is interesting to note that the figures for women are lower than those obtained for schoolchildren from 6 to 16 years of age in New York City.

The group of foreigners gives an average surface ratio of vital capacity of 2.39. This is low as compared with West's standard, seven of the twenty-five being below 90 per cent. The height ratio of 25.1 for the group equals the standard for Americans. The group, as a whole, which includes several overweight and quite sedentary persons, is more than 15 per cent greater in both surface and height ratios than the Chinese. As the measurements were taken under the same conditions, a racial factor is strongly suggested. No vital capacity studies on

TABLE 1—*A Comparison of the Vital Capacity Measurements of Eleven Occupational Groups of a Total of Five Hundred Chinese*

Group	No	Average Vital Capacity, Cc	Average Height, Cm	Average Weight, kg	Average Body Surface, Liters per Sq M	Surface Ratio, Liters per Sq M	Height Ratio, Cc per Cm
Soldiers	97	3,070	164 0	58 0	1 63	1 89	18 8
Police men	40	3,270	163 0	53 4	1 55	2 09	19 7
Workmen	49	3,160	162 0	54 0	1 55	2 03	19 5
Shop clerks	40	2,840	161 0	49 1	1 49	1 90	17 6
House coolies	43	3,320	161 0	54 8	1 56	2 12	20 5
Ricksha coolies	40	3,090	160 0	53 8	1 54	2 01	19 3
Carrying coolies	40	3,240	165 0	56 8	1 61	2 01	19 7
Glassblowers	40	3,280	162 0	52 3	1 54	2 13	20 3
Students	36	3,520	167 0	55 2	1 60	2 18	21 0
Average of	425	3,180	163 0	54 7	1 58	2 02	19 5
Women	75	2,240	157 0	47 7	1 45	1 54	14 3
Foreigners	25	4,360	174 0	69 6	1 83	2 39	25 1

TABLE 2—*Percentage Relation of Surface Ratios to Standards*

Group	No	Average Surface Ratio, Liters per Sq M	% Local Stan- dard, 2 Liters per Sq M	Above 110 per Cent		Below 90 per Cent		Below 80 per Cent		% West's Stan- dard 2 5 Liters per Sq M	Below 90 per Cent	
				No	Per Cent	No	Per Cent	No	Per Cent		No	Per Cent
Soldiers	97	1 89	95	7	7	31	32	15	15	75	94	97
Policemen	40	2 09	105	16	40	8	20	2	5	84	28	70
Workmen	49	2 03	102	9	18	8	16	1	2	81	44	90
Clerks	40	1 90	95	8	20	12	30	6	15	76	33	82
House coolies	43	2 12	106	15	35	1	2			85	31	72
Ricksha coolies	40	2 01	100	12	30	9	22	4	10	80	30	75
Carrying coolies	40	2 01	100	11	28	10	25			80	30	75
Glassblowers	40	2 13	107	16	40	2	5	2	5	85	28	70
Students	36	2 18	109	17	47	2	6			87	22	61
Average of	425	2 02	101	111	26	83	19	30	7	81	340	80
Foreigners	25	2 39	119	20	80	1	4			95	7	28
			Local Standard, 1 5 Liters per Sq M							West's Standard, 2 Liters per Sq M		
Women	75	1 54	102	22	29	15	20	3	4	72	64	85

TABLE 3—*Percentage Relation of Height Ratios to Standards*

Group	No	Average Height Ratio, Cc per Cm	Local Stan- dard, 19 per Cm	Above 110 per Cent		Below 90 per Cent		Below 80 per Cent		West's Stan- dard 20 per Cm	Below 90 per Cent	
				No	Per Cent	No	Per Cent	No	Per Cent		No	Per Cent
Soldiers	97	18 8	99	17	18	25	26	11	11	75	92	95
Police men	40	19 7	104	20	50	10	25	2	5	79	35	87
Workmen	49	19 5	103	15	30	8	16	1	2	78	47	96
Clerks	40	17 6	90	7	17	17	42	9	22	70	40	100
House coolies	43	20 5	108	17	39					80	35	81
Ricksha coolies	40	19 3	101	12	30	9	22	3	7	77	36	90
Carrying coolies	40	19 7	104	12	30	7	17			78	34	85
Glassblowers	40	20 3	107	15	38	4	10	2	5	81	31	78
Students	36	21 0	111	19	53	3	8			84	24	67
Average of	425	19 5	102	134	31	83	19	28	7	78	374	88
Foreigners	25	25 1	132	21	84					100	6	24
Women	75	14 3	Local Standard, 14 Cc per Cm	22	29	17	23	5	7	West's Standard, 20 Cc per Cm	70	93

# BLOOD SUGAR REACTION FOLLOWING INTRAVENOUS INJECTION OF GLUCOSE <sup>1</sup>

L G RIGLER, MD, AND H L ULRICH, MD <sup>2</sup>

MINNEAPOLIS

The literature dealing with the alimentary glucose tolerance test <sup>1</sup> has been recently reviewed by Macleod,<sup>2</sup> Folin and Berglund,<sup>3</sup> John,<sup>4</sup> MacLean and de Wesselow.<sup>5</sup> In addition to its use as a diagnostic aid in diabetes, according to Sherrill,<sup>6</sup> John<sup>4</sup> and others, it has assumed importance in a wide variety of diseases.<sup>7</sup> Janney and Isaacson<sup>8</sup> have improved on the technic as first applied. By doing both blood and urine sugar analyses, the factor of renal permeability has been overcome so that it is rather a reading of glycemia than of glycosuria. In addition, the amount of glucose to be given varies with the weight of the person.

Intestinal absorption, as a variable factor, has long been recognized. Janney and Isaacson<sup>8</sup> discuss this at length and point to the work of Janney<sup>9</sup> and of Fisher and Wishart<sup>10</sup> to prove that it is unimportant. Their proof is not convincing. They state that 66 per cent of the ingested glucose will be absorbed within an hour. The constancy of the blood sugar curve obtained in normal persons is also used as an indication that the absorption is fairly constant. Woodyatt<sup>11</sup> and Wilder and Sansum<sup>12</sup> have called attention to the time element in the metabolism of carbohydrates. If the absorption time is inconstant, the test as ordinarily done, by giving the glucose by mouth, leaves this time

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\* From the University Division of the Minneapolis General Hospital and the Graduate School of the University of Minnesota.

1 The term "tolerance test" is used here only to correlate this work with that previously done on this subject. It is hardly justifiable from our meager knowledge of carbohydrate metabolism to term this a test of glucose tolerance. We feel that it should rather be called the "blood sugar reaction to glucose" as that expresses our actual knowledge of the processes taking place.

2 Macleod, J J R. *Physiol Rev* **1** 208, 1921.

3 Folin and Berglund. *J Biol Chem* **51** 413, 1922.

4 John, H J. *J Metabolic Res* **1** 498, 1922.

5 MacLean and de Wesselow. *Quart J Med* **14** 103, 1921.

6 Sherrill, J W. *The Diagnosis of Latent or Incipient Diabetes*, *J A M A* **77** 1779 (Dec 3) 1921.

7 Olmsted, W H, and Gay, L P. *Study of Blood Sugar Curves Following a Standardized Glucose Meal*, *Arch Int Med* **29** 384 (March) 1922.

8 Janney, N W, and Isaacson, V I. *A Blood Sugar Tolerance Test*, *J A M A* **70** 1131, 1918.

9 Janney, N W. *J Biol Chem* **22** 203, 1915.

10 Fisher and Wishart. *J Biol Chem* **13** 49 1912.

11 Woodyatt, R T. *Harvey Lectures*, **11** 326, 1915.

12 Wilder, R M, and Sansum, W D. *A Glucose Tolerance in Health and Disease*, *Arch Int Med* **19** 311, 1917.



other Eastern races have been found for comparison. It has been noted, however, that the figures for negro children in the United States are less than for the white children of the same ages.<sup>5</sup>

In this study, the height ratios give nearly as uniform results, although there is more variation in the extremes. This method is simpler, and for rapid calculation in clinical work is probably preferable.

Figures obtained for Chinese in Central China will not necessarily hold true for the whole country, since there is a great difference in the stature and physical development of the different races of the Chinese.

#### SUMMARY

1 The vital capacity in 500 Chinese in eleven occupational groups, including a number of young women, has been studied and analyzed.

2 A normal standard of 2 liters per square meter of body surface for men and 1.5 for women was obtained.

TABLE 4—*Summary of Normal Standards*

	Vital Capacity Body Surface, Liters per Square Meter	Vital Capacity Height, Cc per Centimeter
Americans		
Men <sup>4</sup>	2.5	25.0
Women <sup>4</sup>	2.0	20.0
Children <sup>5</sup>	1.93	15.5
"Athletes" <sup>4</sup>	2.8	29.0
Chinese		
Men	2.0	19.0
Women	1.5	14.0

3 A normal standard of 19 c c per centimeter of body height for men and 14 for women may also be used with little less accuracy.

4 Various factors were noted which affect the vital capacity: (a) Men show a vital capacity 31 per cent greater than women. (b) Occupations seem to influence the vital capacity to some extent, although not in proportion to the degree of physical activity. (c) Athletics tend to increase the vital capacity.

#### CONCLUSIONS

The Chinese show much lower vital capacity ratios than Westerners.

Standards based on a picked group of persons cannot be applied uniformly to all groups.

Woodyatt<sup>11</sup> and Wilde<sup>1</sup> and Sansum<sup>12</sup> introduced timed intravenous injections by means of an electric pump. They gave varying amounts of glucose solutions of different concentrations within definite time limits and determined the amount which could be given per hour without glycosuria. They did not, however, attempt to show the amount of hyperglycemia which resulted. Allen and Wishart<sup>22</sup> gave glucose intravenously to partially and completely depancreatized dogs and concluded that the method is a good one for making tolerance tests if the blood sugar estimations are properly controlled by urine examinations. If too much sugar appears in the urine, it may cause a distinct depression in the blood sugar. Titus and Givens<sup>23</sup> have given glucose intravenously to women with toxemia of pregnancy in 20 to 25 per cent solution and have plotted blood sugar curves. Opitz,<sup>24</sup> Beumer,<sup>25</sup> and Nonnenbruch and Szyska<sup>26</sup> have recently made sugar tolerance tests in this way. The latter also have followed the red blood corpuscle count, the serum albumin, the serum sodium chlorid, and the relative volume percentage of the serum and corpuscles. They found definite evidences of a hydremia following the glucose injections. All their cases showed also a rise in the blood sugar shortly after the injection, followed by a drop to normal in most cases.

In the hope of devising a glucose tolerance test which would be free from the variable and uncertain factor of gastro-intestinal absorption, we have given 20 per cent solutions of glucose intravenously to a number of nondiabetic and diabetic persons taken from the medical wards of the Minneapolis General Hospital. All the tests were performed on a basal level, at least sixteen hours after the last food had been taken. The glucose given was a highly purified dextrose, dissolved in distilled water, filtered and sterilized in an autoclave for thirty minutes under 10 to 15 pounds (4.5 to 6.8 kg.) of pressure. The solution was given by means of the pressure flask of Hoffman and Haben,<sup>26</sup> carefully graduated and timed in such a manner that the flow was fairly constant, the amount and the time in which it was given, exact. Other methods of giving timed intravenous solutions have been described by Freidell,<sup>27</sup> Thalheimer,<sup>28</sup> and Korbsch,<sup>29</sup> but we have

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22 Allen and Wishart. *J Biol Chem* **42** 415, 1920.

23 Titus, P., and Givens, M. H. *Intravenous Injections of Glucose in Toxemia of Pregnancy*, *J A M A* **78** 92, 1922.

24 Opitz, H. *Klin Wchnschr* **1** 117, 1922.

25 Beumer, H. *Zschr f Kinder* **29** 352, 1921.

26 Hoffman, M. H., and Haben, H. C. *Transfusion of Citrated Blood*, *J A M A* **76** 358 (Feb 5) 1921.

27 Freidell, H. F. *Apparatus for Continuous Intravenous Administration of Fluids by Which the Rate of Flow May Be Easily Determined and Controlled*, *J A M A* **76** 724 (March 12) 1921.

28 Thalheimer, W. *A Simple Apparatus for Accurate Intravenous Administration of Glucose Solutions*, *J A M A* **78** 190 (Jan 21) 1922.

29 Korbsch, R. *Munchen med Wchnschr* **67** 936, 1920.

factor out entirely<sup>13, 14</sup> The best evidence submitted to show that gastro-intestinal absorption is exceedingly variable is the recent work of Fitz and his co-workers<sup>15</sup> One hour after giving 100 gm of glucose, they passed a duodenal tube into the stomach and aspirated as much of the stomach contents as possible, titrating it for glucose They recovered from 22 per cent to 68 per cent of the amount given, the results in all cases being very different and the variability appearing to be due to individual idiosyncrasy rather than to any rule They also gave varying amounts in solutions of different percentages with an even greater variation in the amount recovered at the end of an hour

Goldschmidt's<sup>16</sup> review of the subject of intestinal absorption is sufficient to show how many factors enter into it and how variable it must be in different persons Bergmarck<sup>17</sup> and Mertz and Rominger<sup>18</sup> have demonstrated the difference it might make in tests on children The latter gave glucose by mouth and plotted a curve of the blood sugar reaction They repeated the test on the same persons under similar conditions except that tannic acid was added to the glucose The curves obtained were radically different, the first being much higher than the second The tannic acid, apparently by its astringent action, had caused a decreased absorption with a slower flooding of the circulation and thus a lower blood sugar curve

If the factor of gastro-intestinal absorption is of such importance, it is obvious that many of the tests done are worthless To overcome this factor and for experimental purposes, glucose has been given subcutaneously, intramuscularly and intravenously The first two methods are, of course, affected by the uncertain factor of absorption The old and recent literature on intravenous glucose injections has been amply reviewed by Wilder and Sansum,<sup>12</sup> Kleiner,<sup>19</sup> Nonnenbruch and Szyszka<sup>20</sup> and Bang<sup>21</sup> Blumenthal,<sup>13</sup> in 1904, attempted to determine glucose tolerance by the intravenous method, but he made no blood sugar estimations, depending on the production of glycosuria and leaving out of consideration the permeability of the kidneys In 1913, Tannhauser and Pfister<sup>14</sup> made the first clinical attempt to determine the hyperglycemia caused in man by the injection of small amounts of glucose solution into a vein They plotted curves for normal persons, persons with chronic nephritis, liver diseases and diabetes In 1916,

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13 Blumenthal, F Beitr z chem Phys u Path **6** 329, 1905

14 Tannhauser and Pfister Munchen med Wchnschr **9** 2155, 1913

15 Beeler, Bryan, Cathcart and Fitz J Metabolic Res **1** 549, 1922

16 Goldschmidt, S Physiol Rev **1** 421, 1921

17 Bergmarck Jahrb f Kinder **80** 373, 1914

18 Mertz and Rominger Arch f Kinder **69** 81, 1921

19 Kleiner, I J Exper M **23** 507, 1916

20 Nonnenbruch and Szyszka Arch f Exper Path u Pharm **86** 281, 1920

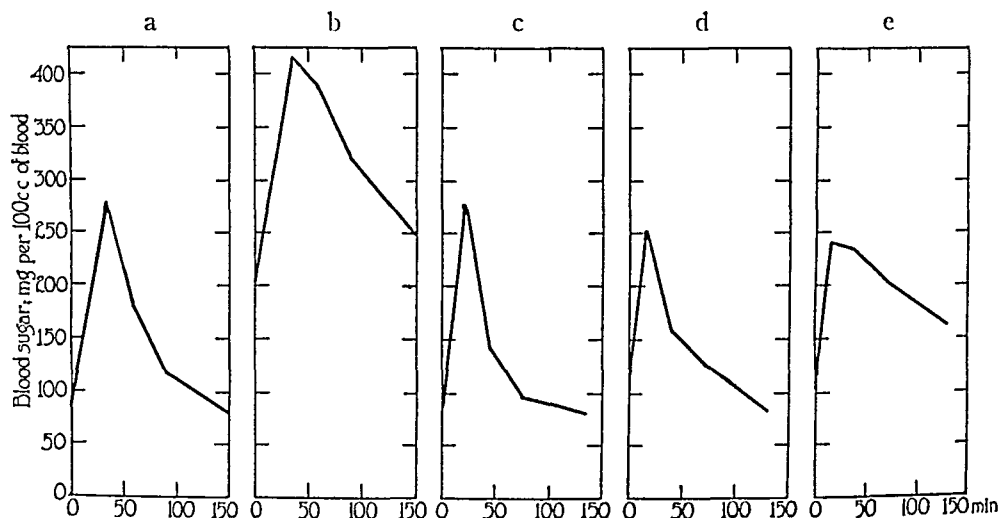
21 Bang, I C Der Blutzucker, Wiesbaden, 1913

hydremia occurred, in accordance with the findings of Fisher and Wishart,<sup>10</sup> Sherrill and John,<sup>30</sup> Nonnenbruch and Szyszka<sup>20</sup> and others

The cases are divided into three groups. The first (Table 1), including ten nondiabetic and five diabetic patients, were given 1 gm of glucose per kilogram of body weight, the duration of the injection being 30 minutes. The second group (Table 2), including thirteen nondiabetic patients, were given 0.5 gm of glucose per kilogram of body weight in fifteen minutes. The third group (Table 3), including seven nondiabetic and three diabetic patients, were given 0.33 gm of glucose per kilogram of body weight in ten minutes. A 20 per cent solution was used throughout. The tables given below show the results obtained. Blood sugar is tabulated in milligrams per one hundred cubic centimeters of blood. Red blood corpuscle counts are tabulated on a basis of percentages, the count before injection being considered as 100 per cent. The quantity of sugar appearing in the urine, the total amount of glucose given, the age of the patient, and the diagnosis of each case are also shown. Five curves have been plotted to illustrate each type of case. All are shown in the chart. The first (*a*) is Case 4, a nondiabetic patient, given 1 gm of glucose per kilogram of body weight in thirty minutes. The second (*b*) is Case 12, a diabetic given 1 gm of glucose per kilogram of body weight in thirty minutes. The third (*c*) is Case 19, a nondiabetic patient given 0.5 gm glucose per kilogram of body weight in fifteen minutes. The last two were given 0.33 gm of glucose per kilogram of body weight in ten minutes. The fourth (*d*) represents Case 29, a nondiabetic patient. The fifth (*e*) represents Case 37, a diabetic patient.

It can readily be seen from the red blood corpuscle counts that in most cases, at least, a hydremia occurs which has a tendency to decrease in direct ratio to the decrease in blood sugar. The characteristic finding in regard to the blood sugar is the marked rise occurring just after the injection, followed by a definite fall to normal usually within one hour, and almost invariably a fall to subnormal at the end of two hours. It appears that the latter is just as important and constant as any of the other characteristics of the normal curve. It is difficult to make a statement from these cases as to the normal curve, because they are not true normals. However, it can be concluded from the examination of all the curves that the normal should show a high rise in the blood sugar just after the injection, a drop to about 50 per cent above the fasting level at the end of thirty minutes, a normal reading at sixty minutes, and a subnormal reading at one-hundred twenty minutes. The diabetic patients show the results which can be expected. The rise just after the injection is much

found the pressure flask eminently satisfactory. It is obvious that the electric pump would be the best method, but this is not generally obtainable. The first sample of blood was collected through the same needle through which the dextrose solution was injected. A second sample was collected five minutes after the injection was completed, a third, thirty minutes after, a fourth, sixty minutes after, a fifth, one hundred and twenty minutes after. Urine was collected for this whole period and for twenty-four hours after in most cases and examined for sugar by the well-known Benedict quantitative method. The samples of blood were all obtained by venipuncture, collected in sodium oxalate, and analyzed shortly after for sugar by the Benedict modification of the Lewis-Benedict method. On many of the cases, separate determinations of whole blood and plasma were made. We



Typical curves from each group of cases illustrating blood sugar reaction of nondiabetic and diabetic to intravenous glucose administration. Blood sugar expressed in milligrams per 100 cubic centimeters of blood on ordinates. Time elapsing from beginning of injection to the collecting of the blood expressed in minutes on abscissas. *A* indicates nondiabetic patients given 1 gm of glucose per kilogram of body weight in thirty minutes (Case 4, Table 1), *B*, diabetic patient given 1 gm of glucose per kilogram of body weight in thirty minutes (Case 12, Table 1), *C*, nondiabetic patient given 0.5 gm of glucose per kilogram of body weight in fifteen minutes (Case 19, Table 2), *D*, nondiabetic patient given 0.33 gm of glucose per kilogram of body weight in ten minutes (Case 29, Table 3), *E*, diabetic patient given 0.33 gm of glucose per kilogram of body weight in ten minutes (Case 37, Table 3).

found that we could not centrifuge the blood rapidly enough to prevent the interchange which takes place rapidly in vitro between corpuscles and plasma. The results were interesting but were no doubt inaccurate and therefore are not published. In most of the cases red blood corpuscle counts were made at the same time that the blood was collected for sugar analysis. This was done to determine whether or not

TABLE 2—Results on Thirteen Nondiabetic Persons given 0.5 Gm Glucose per Kilogram of Body Weight in 20 Per cent Solution Intravenously in Fifteen Minutes \*

Case Number	Specimen Numbers †										Urine Sugar, Gm	Body Weight, Kg	Glucose, Total Amount, Gm	Age of Patient	Remarks
	1		2		3		4		5						
	Blood Sugar, Mg	Red Blood Corpuscles, %	Blood Sugar, Mg	Red Blood Corpuscles, %	Blood Sugar, Mg	Red Blood Corpuscles, %	Blood Sugar, Mg	Red Blood Corpuscles, %	Blood Sugar, Mg	Red Blood Corpuscles, %					
16	98	100	205	65	228	79	124	83	54	93	1	60	30	73	Care noma of stomach
17	155	100	182	77	116	83	91	89	85	95	0	52	26	46	Syphilitic aortitis
18	76	100	240	74	124	79			76	85		48	24	50	Cardiac hypertrophy, chronic asthma, No 4 lost
19	87	100	279	92	145	83	98	81	81	79	2 2	55	27 5	23	Exophthalmic goiter
20	122	100	328	91	207	80	146	86	111	92		45	22 5	76	Hypertension, cardiac hypertrophy, arteriosclerotic nephritis
21	101	100	273	77	125	84			77	88	1	60	30	79	Essential hypertension, No 4 not taken, No 5 at 90 minutes
22	145	100	242	79	206	84	183	86	161	95		80	40	60	Hypertension, cardiac hypertrophy
23	122	100	234	76	211	76	132	85	121	93		82	41	53	Cardiac hypertrophy, syphilis
24	107	100	214	84	143	96			86	98		80	40	73	Chronic arthritis, No 4 not taken, No 5 at 90 minutes
25	110	100	340	81	230	72			92	81		43	21 5	75	Chronic bronchitis, No 4 not taken
26	104	100	306	81	241	81	178	81			0 5	35	17 5	55	Chronic tuberculosis, No 5 not taken
27	76	100	338	96	171	85	107	97	65	101		80	40	72	Senility, fractured femur
28	107	100	285	81	138	90	86	95	80	96	0	68	34	43	Scleroderma, No 5 taken at 90 minutes

\* Blood sugar recorded in milligrams per hundred cubic centimeters of blood. Red blood corpuscle counts made at the same intervals as the blood sugar are charted on a percentage basis, the first count being considered 100 per cent. Urine sugar for the whole period is shown, as well as the total quantity of glucose given. The diagnosis and age of each case are tabulated.

† Blood sugar determinations No 1, before injection, No 2, five minutes after, No 3 thirty minutes after, No 4, sixty minutes after, No 5, 120 minutes after.

TABLE 1—Results on Ten Nondiabetic and Five Diabetic Persons Given 1 Gm Glucose per Kilogram of Body Weight in 20 Per Cent Solution Intravenously in Fifteen Minutes

Case Number	Specimen Numbers †										Urine Sugar, Gm	Body Weight, Kg	Glucose, Total Amount, Gm	Age of Patient	Remarks
	1		2		3		4		5						
	Blood Sugar, Mg	Red Blood Corpuscles, %	Blood Sugar, Mg	Red Blood Corpuscles, %	Blood Sugar, Mg	Red Blood Corpuscles, %	Blood Sugar, Mg	Red Blood Corpuscles, %	Blood Sugar, Mg	Red Blood Corpuscles, %					
1	125	100	436	78	333	92	279	82	104	92	8.64	75	75	38	Acute arthritis, convalescent
2	145	100	325	83	121	91	111	96	79	83	1.5	62	62	40	Acute arthritis, convalescent
3	80	100	307	72	266	82	121	91	78	89	1.1	70	70	39	Chronic bronchitis
4	85	100	279	98	185	70	121	80	80	105	Trace	52	52	67	Chronic bronchitis, syphilis
5	118	100	434	99	300	93	157	94	65		3.25	75	75	65	Essential hypertension, cardiac hypertrophy
6	101	100	320	87		91	192	94	88	102		55	55	54	Cardiac valvular disease, No 3 lost
7	86	100	226	93	205	93	143	96	95	113	4.04	52	52	11	Pleurisy, tuberculous
8	124	100			272	75	212	55	135	75	1.05	61	61	18	Syphilitic cirrhosis of liver slight temperature reaction
9	97	100	151	74	115	95	87		82	110	0.0	45	45	60	Carcinoma of stomach, with metastasis to bowels, cachexia
10	101	100	356	72	255	63	154	71	56	91		71	71	40	Obstructive jaundice, syphilis, cholelithiasis
11	164	100	280	95	318	110	234	86	124	102	8.4	67	67	42	Very mild diabetes
12	204	100	416	84	390	105	323	120	251	104	4.1	47	47	24	Moderately severe diabetes
13	212	100	340	82	315	87	311	81	307	90	10.7	50	50	61	Severe diabetes
14	333	100	466	85	403	90	358	96	314	97	15.0	50	50	45	Severe diabetes
15	461	100	727	76	533	87	492	92	492	91	10.0	40	40	50	Very severe diabetes

\* Blood sugar recorded in milligrams per hundred cubic centimeters of blood. Red blood corpuscle counts made at the same intervals as the blood sugar are charted on a percentage basis, the first count being considered 100 per cent. Urine sugar for the whole period is shown, as well as the total quantity of glucose given. The diagnosis and age of each case are tabulated.

† Blood sugar determinations: No 1, before injection; No 2, five minutes after; No 3, thirty minutes after; No 4, sixty minutes after; No 5, 120 minutes after.

can be considered normal in the strictest sense of the word, as they were taken from the wards, and we have classified them simply as diabetic and nondiabetic. For this reason we do not feel justified in presenting any of these results as definitely indicative of the normal reaction.

As we have plotted no definite normal curve, we hesitate to call attention to the curves presented by the various types of cases. In addition, our series of each type is too small to permit of drawing any conclusions. Our object in this work has been rather to determine whether the method is feasible and, in a general way, what the response would be on the part of the patient. The curves of a large series of normal patients should be determined by this method, following which the curves typical of different diseases might be plotted.

Many objections can no doubt be raised against this method of making sugar tolerance tests. Janney and Isaacson<sup>9</sup> object to the venipunctures, but this is hardly valid, as these are necessary in doing any but the micro tests for blood sugar. The objection that this method is not physiologic in that it leaves the portal system out of consideration, is more difficult to answer. It has been shown by Tannhauser and Pfitzer<sup>14</sup> that the liver plays an important part in the disposition of glucose even when injected intravenously, as their most abnormal curves were obtained in diseases of the liver. Folin and Beiglund<sup>1</sup> point out that the tissues of the body, as a whole, play fully as important a part in carbohydrate metabolism as the liver. The chief objection that must be answered is that the injection of glucose solutions into a vein is not a harmless procedure and should therefore not be indulged in at random. The use of a purified dextrose, well dissolved and sterilized, should obviate any danger. Budingen<sup>31</sup> has given 4,500 injections for therapeutic purposes without one untoward result. Kausch,<sup>32</sup> Korlsch,<sup>33</sup> Lyon,<sup>34</sup> and Haden,<sup>35</sup> and a host of others report similar results. In our own series, we have had only one case in which there was a slight chill followed by a temperature of 99.2 F. In addition to this, two patients who were having an intermittent temperature showed rises of temperature to 100 and 100.4 F, respectively, but it is doubtful that these could be assigned to the glucose injections. The difficulty in giving the intravenous solution can also be considered an objection, but with a little practice it can be done with facility.

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31 Budingen, T. *Deutsch Arch f klin Med* **128** 151, 1918.

32 Kausch, W. *Deutsch med Wchnschr* **37** 8, 1911.

33 Korlsch, R. *Deutsch med Wchnschr* **47** 332, 1921.

34 Lyon, G. *Arch Pediat* **36** 161, 1919.

35 Haden, R. L. *Therapeutic Application of the Alteration of Brain Volume by the Intravenous Injection of Glucose*, *J A M A* **73** 983 (Sept 27) 1919.



higher, there is only a small depression at the end of thirty minutes, at the end of sixty minutes the blood sugar is still far above the fasting level, at the end of 120 minutes it is still above the fasting level or just at it. The difference between the normal persons and the mild diabetic patient can be seen by a comparison of the curves shown. The curves as a whole resemble those obtained by the alimentary method, but the action is more rapid.

We do not feel that, in the consideration of this test, the excretion of sugar in the urine is an important finding, except in so far as a large excretion of sugar be accompanied by a rapid fall in the blood sugar. This does not occur when using the smallest dose, so that it need not be seriously considered. It is of interest to note that in many

TABLE 3—Results on Seven Nondiabetic and Three Diabetic Persons Given 0.33 Gm Glucose Per Kilogram of Body Weight in 20 Per Cent Solution in Ten Minutes\*

Case Number	Specimen Numbers †					Urine Sugar, Gm	Body Weight, Kg	Glucose, Total Amt, Gm	Age of Patient	Remarks
	1	2	3	4	5					
29	119	254	161	131	82	0	57	19	51	Chronic cardiac valvular disease
30	98	220	166		94		66	22	58	Essential hypertension, No 4 not taken
31	96	182	147	87	86	0	60	20	70	Essential hypertension
32	112	272	182		81	0.66	60	20	60	Chronic duodenal ulcer, No 4 not taken
33	80	234	142	117	91		67	22.3	53	Chronic arthritis
34	82	237	174	99	72	0	69	23	68	Bronchial asthma
35	84	200	136	104	88	0	43	14.2	43	Carcinoma of stomach with metastasis to liver
36	163	365	294	233	166	0	81	27	55	Moderately severe diabetes
37	120	241	238	205	164	2	72	17.3	63	Mild diabetes
38	326	601	483	441	365	Trace	43	14.3	63	Severe diabetes

\* Blood sugar recorded in milligrams per hundred cubic centimeters of blood. Urine sugar for the whole period is shown, as well as the total quantity of glucose given. The diagnosis and age of each case are given.

† Blood sugar determinations: No 1, before injection; No 2, five minutes after; No 3, thirty minutes after; No 4, sixty minutes after; No 5, 120 minutes after.

cases in which the blood sugar rose to a figure far above 200 mg per one hundred c.c., no sugar was excreted. This may be due to the fact that the elevation of the blood sugar was too transitory to produce a glycosuria.

The amount of glucose given and the duration of the injection are of course important considerations, as can easily be seen from our results. The three different methods used were purely experimental. We feel that the last method, giving 0.33 gm of glucose per kilogram of body weight in ten minutes is the best, as it is easiest to give, does not cause such marked elevation in the blood sugar, and seldom produces marked glycosuria. It is possible that even smaller doses might be still more desirable. It should be noted that none of the cases used

EXPERIMENTS WITH HODGKIN'S DISEASE  
AN ATTEMPT TO PRODUCE IT IN ANTHROPOIDS AND  
OTHER MONKEYS<sup>1</sup>

W F CUNNINGHAM, M D

AND

KENNETH McALPIN, M D

NEW YORK

These experiments were made in an attempt to produce Hodgkin's disease in chimpanzees and rhesus monkeys. The apes were chosen because numerous attempts were made to produce this disease in lower animals. Feeding experiments and injections of gland extracts have been made on guinea-pigs, rabbits, ring tail and rhesus monkeys<sup>1</sup>. Certain hyperplasias have been produced, but it has been shown that the injection into animals of normal gland extracts causes a lymphatic hyperplasia.

For a working basis the following premises were adopted: 1. Hodgkin's disease is a distinct clinicopathologic entity. 2. It belongs to the group of infectious granulomas and is of bacterial or protozoan origin.

The results obtained were all negative, but it is believed that they should be recorded because the biologic similarity between chimpanzees and man make the findings of more significance in regard to the transmissibility of the disease by implantation of tissue.

ANIMALS

Before procuring the chimpanzees, it was necessary to learn something of the habits and living conditions of these animals, and many months were spent in veterinary consultations and going over plans for proper housing and caging. After securing the animals, the next step was to determine, as far as possible, that they were free from disease. Such conditions as eczema, pyorrhea alveolaris and round worms, were very troublesome. Wassermann tests were made and also complement-fixation tests for tuberculosis. The latter were felt to be important, owing to the susceptibility of apes to this disease. The two chimpanzees gave positive reactions, but they showed no evidence of tuberculosis while under our observation from Oct 28, 1916, until May, 1920.

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\* This work was carried on under a grant from the Harriman research fund.

\* From the laboratories of the department of surgery, Columbia University.

1. Reed, Bull. Johns Hopkins Hosp. No. 10, 1902, p. 135. Longcope, Bulletin Ayer Clinical Lab. No. 4, 1907. Bunting, C. H., and Yates, J. G., An Etiologic Study of Hodgkin's Disease, J. A. M. A. **61**: 1803 (Nov. 15) 1913, An Etiologic Study of Hodgkin's Disease, **62**: 516 (Feb. 14) 1914. Schaeffer, E., Berl. klin. Wchnschr. **51**: 1215, 1914.

The subject has fertile possibilities. We have not attempted to present any definite standards, but merely offer this method as a suggestion for future use. We feel that we have demonstrated its simplicity, feasibility, and its superiority to the alimentary test in determining a variation in carbohydrate metabolism. Intravenous tolerance tests in the past have been so variable in their methods and technic that adequate comparison is impossible. More work should be done by this method to establish standards, and this can only be done if a uniform technic is used. The purpose of this paper has been to suggest such a technic and to demonstrate its applicability to the test.

#### SUMMARY AND CONCLUSIONS

The alimentary glucose tolerance test is objectionable chiefly because of the great variability in gastro-intestinal absorption time rendering it inaccurate and misleading.

The previous work on intravenous glucose tolerance tests is discussed. The methods and technic used by the authors in making glucose tolerance tests by the intravenous method on thirty-eight cases is presented and the results shown in tables and curves.

The differences between the normal reaction of the blood sugar to the intravenous injection of glucose and the diabetic reaction are shown. Glucose tolerance tests can be made far more accurately by giving glucose solutions intravenously and making blood sugar estimations at intervals afterward, than by the alimentary route.

The intravenous injection of glucose is a simple and harmless procedure. Further work should be done by this method to establish normal standards.

## EXPERIMENTAL WORK

*Experiment 1*—A group of three nodes was removed from a man, 23 years of age, who first noticed an enlargement in the neck eight months previously. Later lymphomas developed in the axillae. These showed the typical histologic picture of Hodgkin's disease (Fig. 1).

A slice of a node 1.5 by 0.3 cm. was transplanted into the retroperitoneal region and one 0.7 by 0.5 into the spleen of a rhesus. The animal was observed for five months, and no external evidence of Hodgkin's disease was noted.

The rhesus was then used for a poliomyelitis experiment and died. Necropsy was performed and microscopic examinations were made, but no evidence of Hodgkin's disease was found.

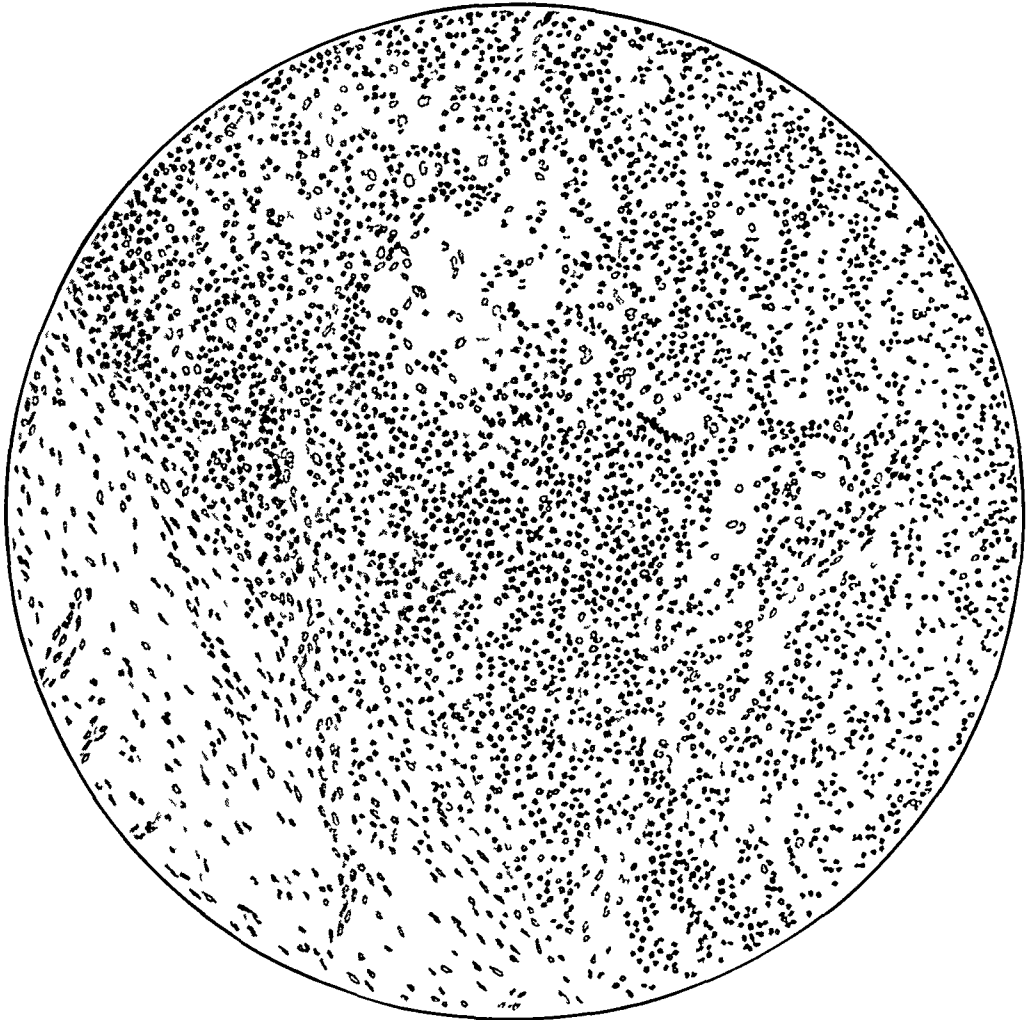


Fig. 3—Low power reproduction of drawing of gland used in Experiment 3.

*Experiment 2*—Glands were removed at the Roosevelt Hospital from the groins of a man, 30 years of age, who had been suffering from weakness, night sweats and lymphomas in the axillae, neck and groins.

Histologically the glands were those of Hodgkin's diseases (Fig. 2).

Bacteriologic examinations were made of the glands, but no organisms were isolated.

Two pieces of nodes 1.5 by 0.4 cm. and 1 by 0.4 by 0.3 cm. were transplanted into the retroperitoneal region and spleen of a young rhesus. The animal was used for a poliomyelitis experiment, and died of abscess of the brain. At

Apparently, tuberculosis runs its almost uniformly fatal course in these animals within eighteen months under the zoologic and circus conditions of New York City



Fig 1—Low power reproduction of drawing of gland used in Experiment 1

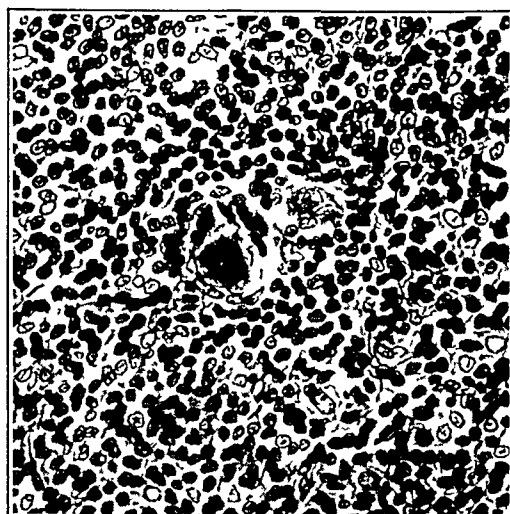


Fig 2—High power reproduction of drawing of gland used in Experiment 2

Both chimpanzees were immature females. They were in the process of shedding their baby teeth and were judged by an expert from the Bronx Zoological Park to be about 4 years of age.

In July, 1919, glands were removed from the cervical region and a slice of gland 3 by 2 by 1 cm transplanted under the deep cervical fascia of a female chimpanzee about 6 years old

The histologic picture was that of Hodgkin's disease (Figs 4 and 5)

Anaerobic and aerobic cultures made from the gland at the time of transplantation revealed *Staphylococcus albus* but the wound healed without infection. The animal was in perfect health two years after the experiment

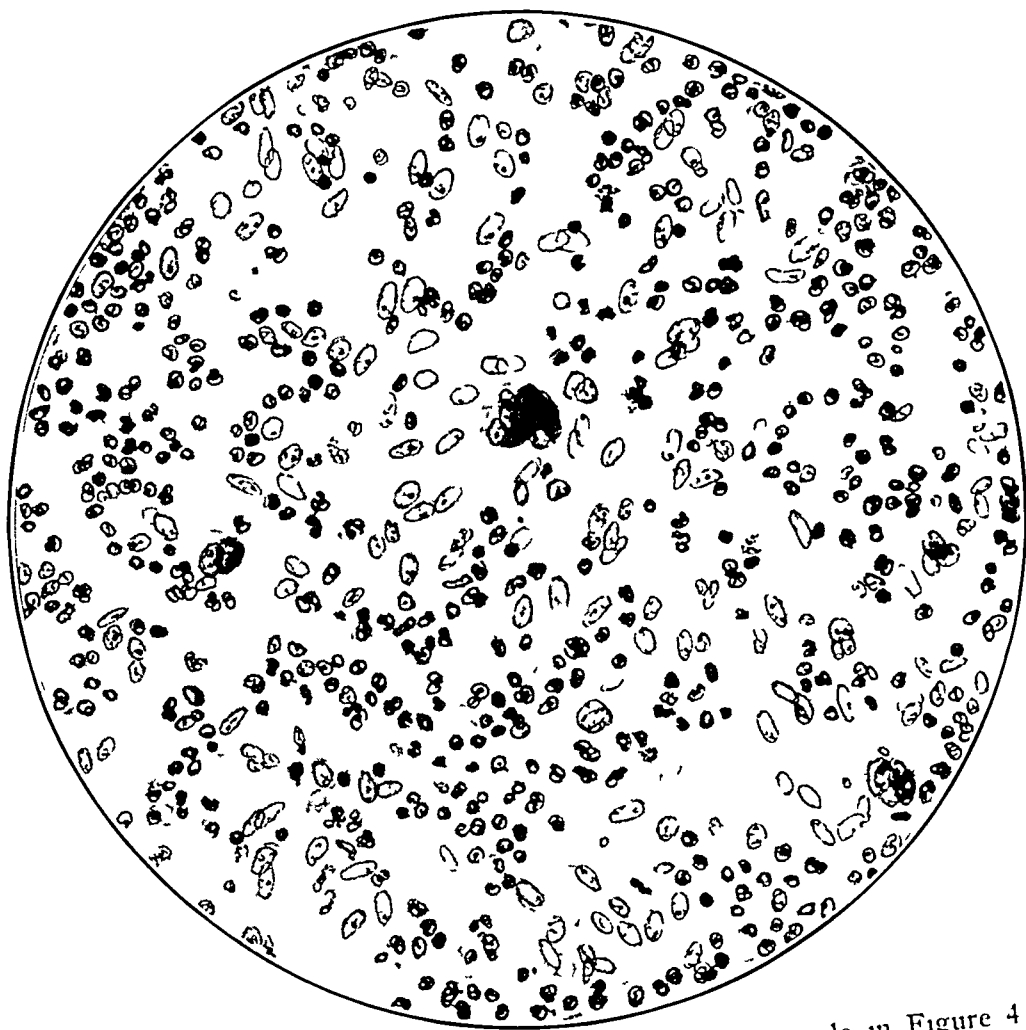


Fig 5—High power reproduction of field within circle in Figure 4

#### COMMENT

The two rhesus monkeys were observed five and six months, respectively, and at necropsy showed no evidence of lymphomas

The two chimpanzees were observed for about two years in our cages after the transplants were made and showed no external evidence of Hodgkin's disease. They were then used as exhibition animals in a circus. The one used in Experiment 3 died in November, 1921, the diagnosis by the veterinary surgeon being tuberculosis. Necropsy was not performed

necropsy no evidence of Hodgkin's disease was found. Histologic examination showed scar tissue in the spleen at the site of transplantation.

*Experiment 3*—Glands were removed from a man, about 37 years of age. This patient showed the first signs of Hodgkin's disease two years previously, and the nodes were removed at that time to confirm the diagnosis.

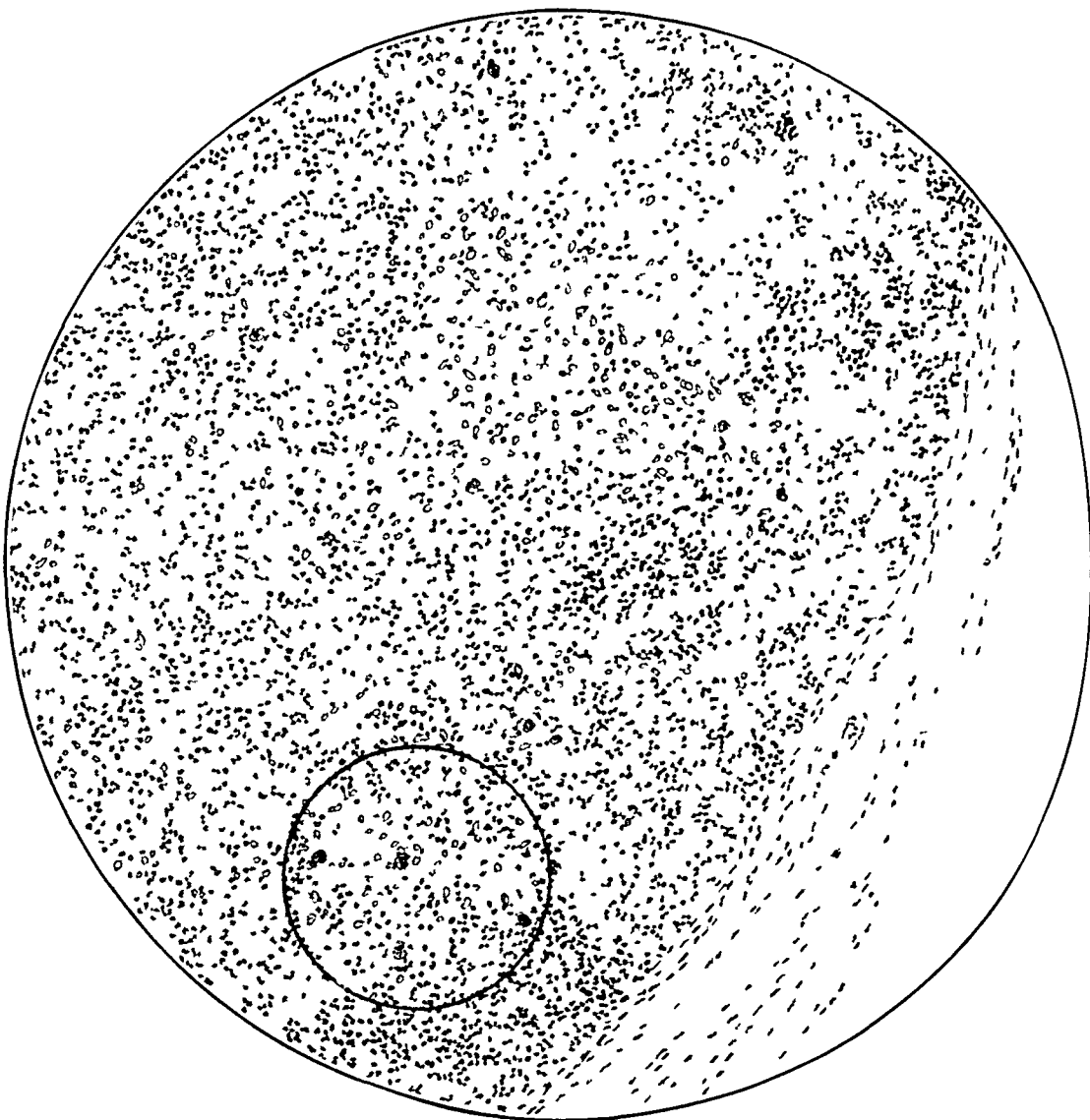


Fig 4—Low power reproduction of drawing of gland in Experiment 4. The part within the circle is represented in Figure 5.

In June, 1919, a gland was removed from the inguinal region, and a section 2 by 1 by 1 cm was transplanted beneath the deep cervical fascia of a female chimpanzee about 6 years old.

Sections made from the gland (Fig 3) were typical of Hodgkin's disease. Cultures made at the time of transplantation revealed diphtheroid bacilli in Petroff's culture medium and broth, and staphylococci in broth. The wound healed without infection. The animal died in November, 1919.

*Experiment 4*—Glands were removed from a boy, aged 15 years, who gave a two years' history of swellings in the right side of the neck and right axilla.

# THE SIZE OF THE HEART IN PNEUMONIA

A TELEROENTGENOGRAPHIC STUDY, WITH OBSERVATIONS ON THE  
EFFECT OF DIGITALIS THERAPY<sup>\*</sup>

ROBERT L. LEVY, MD

NEW YORK

Precise information concerning the behavior of the heart in pneumonia is essential for the rational management of the circulation in this disease. Whether, in the course of acute pneumonitis, the cardiovascular system is functionally impaired, is still a matter of controversy. Direct methods for the estimation of myocardial function are still wanting. But alterations in the size of the heart furnish evidence, although indirect, of changes in the physical state of the myocardium, and in particular of variations in the length of heart muscle fiber. Such changes, as will be pointed out, have been shown by investigation to be associated with alterations in the volume output of the ventricles, and on the maintenance of ventricular volume output depends, in large measure, the efficiency of the circulation as a whole.

The present investigation was designed to obtain, by the roentgenographic method, at relatively frequent intervals, accurate records of the size of the heart in patients ill with pneumonia. The cardiac silhouette was outlined and measured according to a special technic, and an attempt has been made to estimate the significance of the changes observed. The effect of digitalis on the size of the heart has also been studied.

## LITERATURE

It appears that Dietlen<sup>1</sup> is the only observer who has taken accurate records of the size of the heart in pneumonia throughout the course

TABLE 1—*Size of Heart Throughout Disease in Dietlen's Case*

Day of disease	2	3	5	6	7	11	12	14	19	21	24	25
Area, sq. cm.	123	123	133	135	134	123	122	122	122	122	117	116

of the disease. He made orthodiagrams of eleven cases of lobar pneumonia and found cardiac dilatation in four (36.4 per cent). In two of these cases, the enlargement was slight and transitory, in the third

<sup>\*</sup> From the Hospital of the Rockefeller Institute for Medical Research.

<sup>\*</sup> A preliminary report of this work was read before the American Society for Clinical Investigation, May 9, 1921.

<sup>1</sup> Dietlen, H. Orthodiographische Beobachtungen über Veränderungen der Herzgrösse bei Infektionskrankheiten, bei exsudativer Perikarditis und paroxysmaler Tachykardie, nebst Bemerkungen über das roentgenologische Verhalten bei Pneumonie. München med. Wchnschr. 55:2077, 1908.



The second chimpanzee was taken ill about this time, the prominent symptoms being cough, loss of weight and fever. She died Feb 5, 1922. Necropsy was performed forty-eight hours postmortem, the anatomic diagnosis being Tuberculosis and edema of the lungs, tuberculosis of the cervical, tracheal and mesenteric lymph nodes, tuberculosis of the spleen, miliary and caseous, tuberculosis (?) of solitary follicles of the ileum, tuberculosis, miliary, of the liver. Microscopic examination was made of the lungs, lymph nodes, liver, spleen and intestines. The lungs presented an advanced degree of caseation, with the formation of tubercles without giant cells. The lymph nodes and spleen presented a similar picture. The liver presented marked fatty infiltration with pronounced postmortem change and a few small areas of necrosis, the nature of which was not determined. The kidneys also presented postmortem change, but no evidence of tuberculosis. On the mucosal surface of the ileum was a small ulceration with fibrosis and round cell infiltration.

Tuberculosis in chimpanzees is a rapidly fatal disease and there is little doubt that the infection took place after the animals left our cages. We have found no evidence that Hodgkin's disease has been produced in the rhesus monkeys and chimpanzees used in these experiments.

two acute angles of lead were secured anteriorly—one in the supra-sternal notch, the other in the substernal angle. In later plates, the posterior lead strip was omitted, as the vertebral spines could be plainly seen in the negatives. Unclear or improperly aligned records were discarded.



Fig 1—Teleroentgenogram, showing method of taking the plates

*A New Technic for Completing the Outline of the Cardiac Silhouette*—In the plates, the diastolic outline of the right and left borders and the midline were traced on paper. This made possible the measurement of transverse and long diameters. The angle of inclination of the heart—that is, the angle formed by the long diameter and a line drawn to the apex at right angles with the median line—was also recorded. Instead of completing the silhouette by arbitrarily joining

case it was somewhat greater. No figures are given. Measurements of the area are recorded in the fourth case, and are now reprinted, since the changes observed are comparable to those to be reported in this paper.

On the sixth and seventh days of the disease, the patient was very ill. He was first afebrile on the eleventh day. Dietlen remarks that dilatation was coincident with the severest period of the illness—"the dangerous time before crisis."

#### MATERIAL AND METHODS

*Material*—Teleroentgenograms of the chest were made every second day, or at times as nearly approximating this interval as the condition of the patients warranted, of twenty-one cases of lobar pneumonia and eight cases of bronchopneumonia, during the acute stages of the disease and throughout convalescence in the hospital. Two hundred and eighty-four plates were taken and form the basis of this study. Three normal young men and one patient with fever due to acute bronchitis and pulmonary tuberculosis served as controls.

*Method of Taking the Roentgenograms*—The exposures were made for one-half second, during the inspiratory phase of normal respiration, the subjects being in the recumbent position. The plates were at a distance of 2 meters from the anticathode of the roentgen-ray tube. The patient was instructed to breathe as quietly as possible and was unaware of the instant at which the picture was to be taken. In order to record graphically on the plate the phase of respiration in which the exposure was made, a lead strip was secured to the plateholder with adhesive plaster to indicate the neutral position of the vertically hanging lever of a Marey tambour, the lever being tipped with a solid knob of lead. The tambour was connected by means of rubber tubing with a Politzer bag, held in position in the right axilla of the patient by a linen binder, secured by fastening its tails. During respiration, the lever of the tambour swung on one side or the other of the neutral strip. The side to which the lever deviated during expiration was denoted by the letter *E* (Fig. 1). The pictures were obtained during inspiration in a majority of instances. Slight variations in the time of exposure were disregarded, as it has been shown, employing a similar technic, that the difference in the size of the heart during normal inspiration and expiration is so small as to be negligible.<sup>2</sup>

In order to verify the accuracy of anteroposterior alignment, a thin lead strip was placed over the spinous processes of the vertebrae, and

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<sup>2</sup> Cohn, A. E. An Investigation of the Size of the Heart in Soldiers by the Teleroentgen Method, *Arch Int Med* 25:499 (May) 1920.

will be accompanied, in the same sense, by corresponding changes in the areas outlined. The subjective, arbitrary construction formerly employed may, therefore, properly be replaced by one which is objective even though arbitrary in its variations.

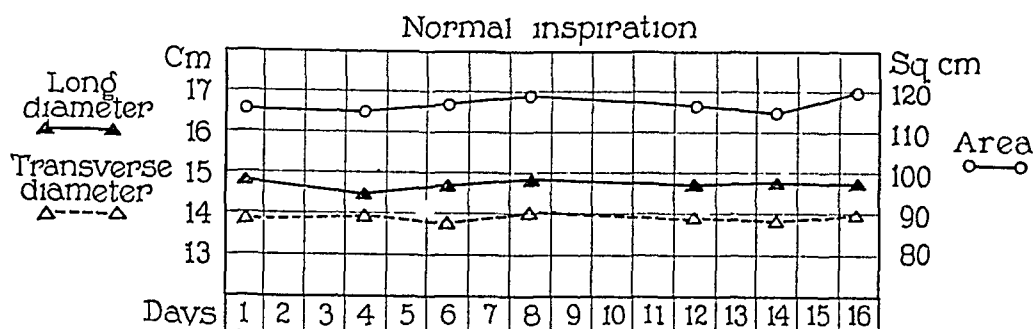


Fig 3—Graph of cardiac measurements in a normal young man, G S, aged 17. Seven plates were made during a sixteen day period.

### CONTROL SERIES

Variations in the cardiac measurements in the same person from day to day may be due either to the fact that significant changes in the size of the heart actually occur under ordinary conditions or to technical errors in the method of measurement. To obtain data on this point, roentgenograms were made, according to the technic described, of three normal young men who were workers in the laboratory. Plates were taken every second or third day until six or seven had been made.

TABLE 2—Exposures Made During Normal Inspiration \*

Date	Horizontal Posture					
	Maximum Right, Cm	Maximum Left, Cm	Transverse Diameter, Cm	Long Diameter, Cm	Area, Sq Cm	Angle Degrees
Feb 18	5.4	7.9	13.3	14.0	111	35
Feb 21	5.2	8.1	13.3	14.1	113	35
Feb 23	5.7	7.7	13.4	14.1	113	37
Feb 25	5.5	7.8	13.3	14.1	113	36
March 1	5.6	7.6	13.2	14.0	111	38
March 3	5.6	7.5	13.1	13.9	109	37
Maximum Variations						
	0.5	0.5	0.3	0.2	4	3

\* These roentgenograms were made of D. W. L., a man, aged 18 years, a normal person.

(Table 2) Measurements of these roentgenograms show that the maximum variation in transverse diameter was 0.6 cm, in long diameter 0.4 cm and in area 8 square centimeters.<sup>3</sup>

3 Measurements of *MR*, *ML* and the angle of inclination are included in the tables for purposes of reference, but will not be alluded to in the discussion.



by mouth, in the form of digitan. Of the eleven patients not receiving digitalis, eight (72.7 per cent) showed cardiac enlargement, of the ten receiving this drug, five (50 per cent) showed cardiac enlargement.

TABLE 3—*Summary of Twenty-One Cases of Lobar Pneumonia Grouped According to Pneumococcus Types*

	Number of Cases	Percentage
Type I	12	57.1
Type II	2	
Type IIA	1	15.1
Type III	1	5.1
Group IV	5	22.7
Type I—12 Cases		
No change in heart size	3	25
Change	9	75
Cases Not Receiving Digitalis—7		
No change in heart size	1	14.3
Change	6	85.7
Cases Receiving Digitalis—5		
No change in heart size	2	40
Change	3	60
Type II and IIA—3 Cases		
No change in heart size (1 received digitalis)	2	66.7
Change	1	33.3
Type III—1 Case		
Change—Digitalis given		
Group IV—5 Cases		
No change in heart size	3	60
Change	2	40
Cases Not Receiving Digitalis—2		
No change in heart size	1	50
Change	1	50
Cases Receiving Digitalis—3		
No change in heart size	2	66.7
Change	1	33.3

TABLE 4—*Summary (284 Plates)*

	Number of Cases	Percentage
Lobar Pneumonia—21 Cases		
No change in heart size	8	38.1
Change	13	61.9
(a) In all measurements	9	
(b) In long diameter and area only	4	
Cases Not Receiving Digitalis—11		
No change in heart size	3	27.3
Change	8	72.7
(a) In all measurements	6	
(b) In long diameter and area only	2	
Cases Receiving Digitalis—10		
No change in heart size	5	50
Change	5	50
(a) In all measurements	4	
(b) In long diameter and area only	1	
Bronchopneumonia—8 Cases		
No change in heart size	6	75
Change	2	25
(Change occurred in all measurements)		
Cases Not Receiving Digitalis or Strophanthin—6		
No change in heart size	4	66.7
Change	2	33.3
Cases Receiving Digitalis or Strophanthin—2		
No change in heart size	2	100
Change	0	

(Table 4) From these facts it appears that (1) in about 62 per cent of these cases of lobar pneumonia, cardiac dilatation occurred during the course of the disease, (2) cardiac dilatation occurred less frequently in the patients who received digitalis than in those who did not.

In order to ascertain the effect of fever and tachycardia on the size of the heart, measurements of the heart were made in a patient with acute bronchitis and pulmonary tuberculosis, but without signs of consolidation in the lungs. The maximum variation in transverse diameter was 0.7 cm, in long diameter 0.2 cm and in area 1 sq cm. That fever and tachycardia per se are not necessarily associated with a change in the size of the heart was later abundantly confirmed by observations on cases of pneumonia in which no alteration was noted (Fig 4)

It seemed reasonable, on the basis of these findings, to regard as a significant change in the outline of the heart a variation of 1 cm or more in one of the diameters, or of 10 sq cm or more in area. Usually,

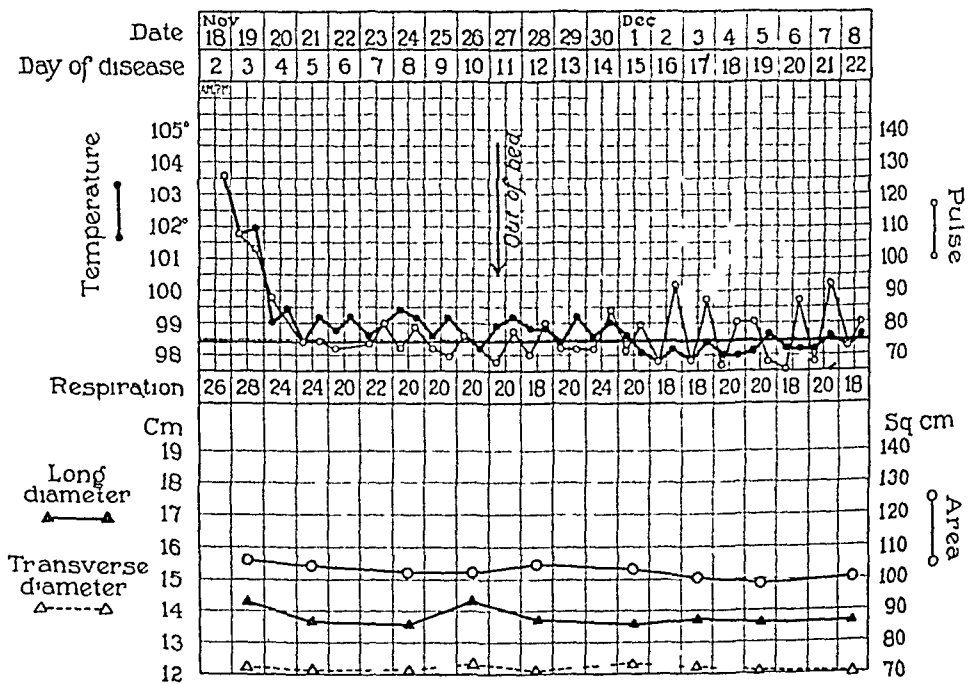


Fig 4 (Case 24) —Clinical chart and cardiac measurements of a woman, A J, aged 27, who had bronchopneumonia of the right lower lobe, pneumococcus, group IV

when a change was observed, it took place in all measurements, and was of a greater order of magnitude than the minimal criteria established

RESULTS IN PNEUMONIA

*Lobar Pneumonia*—The twenty-one cases studied presented varying degrees of severity. Bacteriologic examination of the sputums showed the usual types of organisms (Table 3). The series is too small to permit of generalizations which take into account age and sex. Of the entire group, thirteen patients (61.9 per cent) showed an increase in the size of the heart during the course of the illness. Eleven of the patients did not, however, receive digitalis, to ten this drug was given,

The order of magnitude of the change is of interest (Table 5). In the patients not receiving digitalis, the increase in transverse diameter was from 4.5 to 15.4 per cent (an average of 9.3 per cent), in long diameter from 4.4 to 13.5 per cent (an average of 8.2 per cent), in area from 11.6 to 27.1 per cent (an average of 16.5 per cent). In the digitalized patients who showed enlargement, the increase in transverse diameter was from 3.6 to 19.2 per cent (an average of 11.0 per cent), in long diameter, from 2.6 to 19.7 per cent (an average of

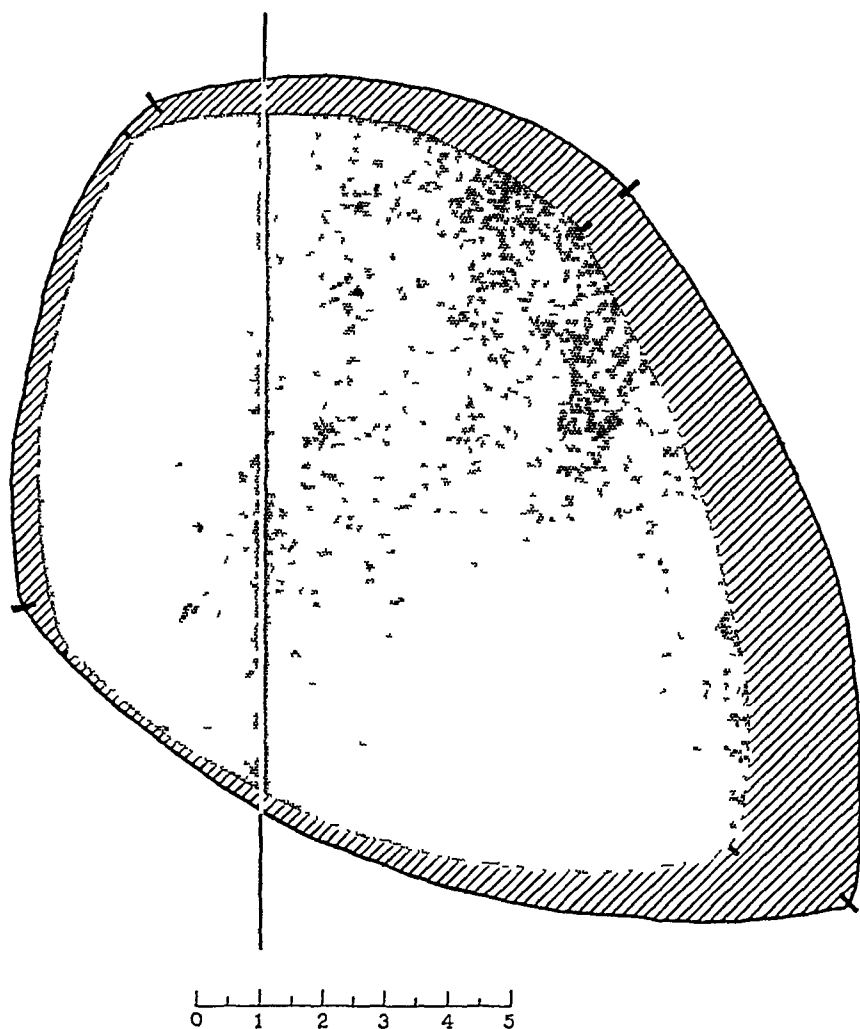
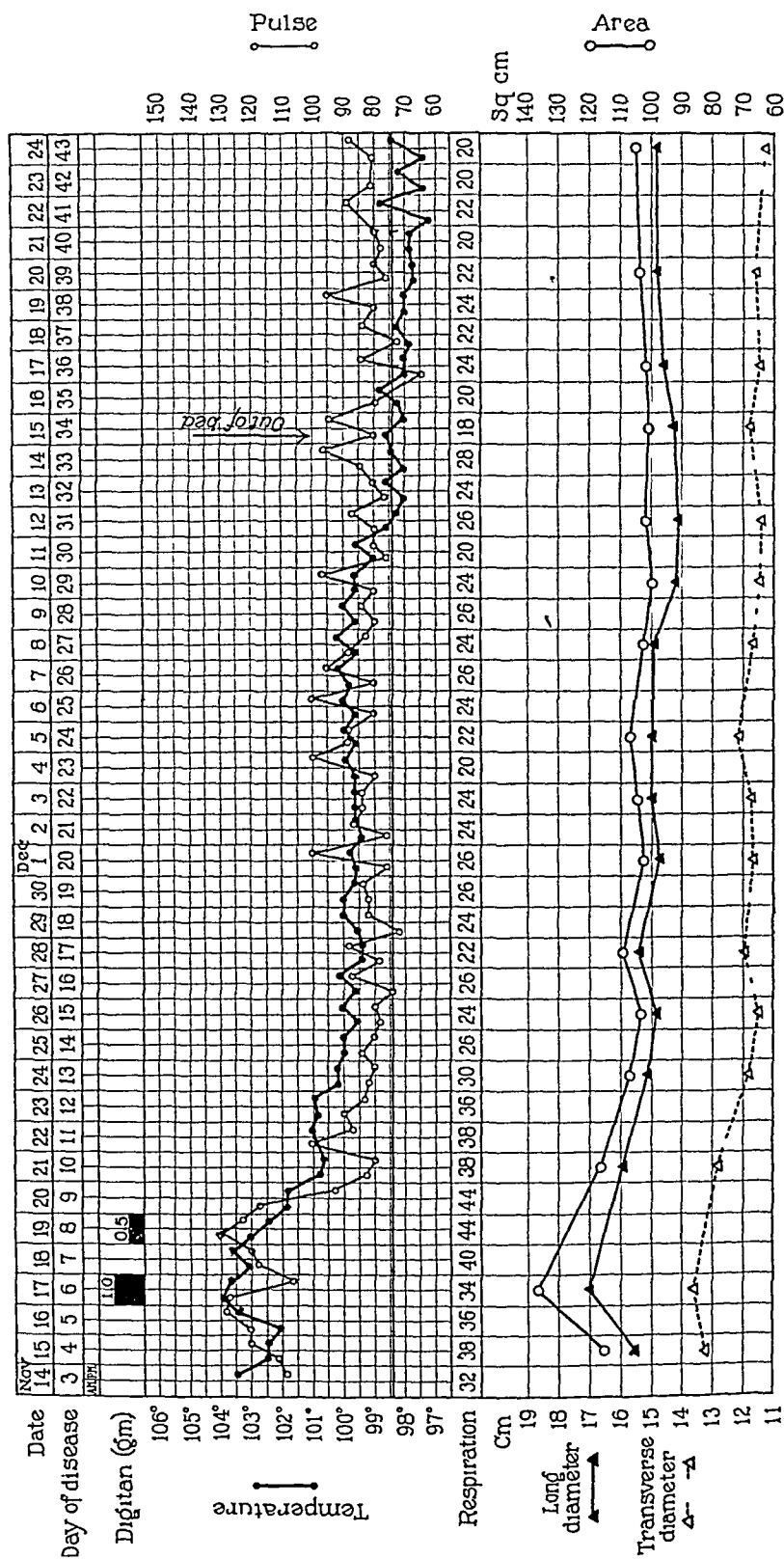


Fig 6 (Case 15) —Silhouettes showing extremes of variation in heart size

10.2 per cent), in area from 11.1 to 37.3 per cent (an average of 18.5 per cent). The differences in the two groups are not striking. The averages in the second group are increased by the figures obtained from a patient with Type III pneumococcus infection involving the entire right lung and the left lower lobe. In this man, critically ill, the transverse diameter fell from 13.6 cm at the height of the disease to 11.4 cm during convalescence, the long diameter from 17.0 to 14.2 cm, the area from 136 square cm to 99 square cm (Figs 5 and 6).





The correspondence in this case between the size of the heart and the clinical condition is striking. Digitalis was not administered until the sixth day of illness, at a time when the patient's life hung in the balance. The temperature from this day on fell by lysis and the heart decreased in size, reaching a constant level on the twentieth day of disease.

As a rule, the increase in heart size was gradual, often reaching its maximum at the height of the disease, but sometimes after the subsidence of fever. The return to a constant level was also gradual, at times lagging behind the fall in temperature and pulse rate (Figs 7 and 8). In a number of cases, there was marked postfebrile decrease in size, the heart at this time being smaller than during later convalescence (Figs 9 and 10). In two instances, one patient receiving digitalis (Case 16), the other (Case 7) not receiving this drug, the heart was distinctly larger during convalescence than during the height of the illness. In both cases there was pronounced bradycardia during the convalescent period.

In the thirteen patients showing increase in the size of the heart, the change was observed in all measurements in nine, in long diameter and area only, in four. The transverse diameter was accordingly the least reliable index of variation. The greatest percentage variation occurred in the area. It is impossible to attempt to determine from the tracings which chamber or chambers of the heart participated in the enlargement. For the method employed measures only a portion of the heart, in a single plane.

*Bronchopneumonia*—Eight cases were studied (Tables 4 and 5). Of these, a change in the size of the cardiac silhouette occurred in two (25 per cent), and was observed in all measurements. In one patient with diffuse, bilateral, streptococcus pneumonia, of whom plates were made until three days before death, there was seen a progressive diminution in the size of the heart (Case 26). No observations were made during the last three days. He received no digitalis.

Of the eight cases, one, a boy of 19 years, received digitalis, beginning on the sixth day of the disease, another, who had mitral stenosis, received 0.7 mg of strophanthin intravenously on the eighth day of illness. Neither of these patients showed a change in the size of the heart. The drugs were given late in the course of the pneumonia so that their influence on the behavior of the heart is a matter of doubt.

In brief, it is apparent that cardiac dilatation is less frequently encountered in bronchopneumonia (25 per cent) than in lobar pneumonia (61.9 per cent). When it occurs as will be seen from Table 5 and from Figures 7 and 8, the change is comparable in degree and

TABLE 5—Summary of Twenty-One Cases of Lobar Pneumonia and Eight Cases of Bronchopneumonia, Showing Relation of Changes in Heart Size to Digitalis Therapy

Case No Name, Age	Bacteri- ology	Lobes In- volved	Heart Size	Maximal Per centage Change			Digi- talis or Stro- phan- thin	Total Amount Given	Day of Dis- ease Drug Begun	Ser- um
				Area	Trans- verse Diam- eter	Long Diam- eter				
1 E M 52	Pneumococcus I Bacillus influenzae	L L	+	162	90	97	0			+
2 M F 29	Pneumococcus I	L L	+	271	122	135	0			+
3 S P 36	Pneumococcus I Bacillus influenzae	L L	+	195	71	105	0			+
4 H D 39	Pneumococcus I	L L	+	116	45	65	0			+
5 P K 19	Pneumococcus I Bacillus influenzae	L L	+	123	58	42	0			+
6 L M 21	Pneumococcus I Bacillus influenzae	R L, L L	+	125	123	71	0			+
7 F T 29	Pneumococcus IV Bacillus influenzae	R L	+	150	85	114	0			
8 T M 47	Pneumococcus IIA	R L	+	185	154	44	0			
9 J K 18	Pneumococcus II	R L, L L	0	0	0	0	0			
10 J S 28	Pneumococcus IV	L L	0	0	0	0	0			
11 S B 13	Pneumococcus I Bacillus influenzae	R U	0	0	0	0	0			0
12 J C 30	Pneumococcus I	R L	+	111	36	26	+	0.6 gm	5	+
13 P O'M 25	Pneumococcus I	R U, R M, R L	+	184	89	88	+	0.8 gm	4	+
14 E D 39	Pneumococcus I	R U, L L	+	147	130	104	+	1.5 gm	4	+
15 A T 29	Pneumococcus III	R U, R L, R M, L L	+	373	192	197	+	1.5 gm	6	
16 F I 32	Pneumococcus IV	L L	+	112	102	97	+	1.5 gm	4	
17 V P 26	Pneumococcus I	R L	0	0	0	0	+	1.5 gm	5	+
18 M L 34	Pneumococcus I Bacillus influenzae	L L	0	0	0	0	+	0.9 gm	2	+
19 L W 16	Pneumococcus II Bacillus influenzae	R L	0	0	0	0	+	1.8 gm	2	
20 A R 37	Pneumococcus IV	R U	0	0	0	0	+	0.9 gm	6	
21 R L 34	Pneumococcus IV Bacillus influenzae	L L	0	0	0	0	+	1.0 gm	2	
Bronchopneumonia										
22 M Q 39	Pneumococcus IV Bacillus influenzae	Dif bilat	+	171	37	52	0			
23 E S 55	Pneumococcus IV	L L	+	298	120	201	0			
24 A J 27	Pneumococcus IV	R L	0	0	0	0	0			
25 G B 13	Streptococcus hemo- lyticus	R L	0	0	0	0	0			
26 O G* 35	Streptococcus hemo- lyticus, Bacillus influenzae	Dif bilat	—	—	—	—	0			
27 M K 19	Pneumococcus IV	R L	0	0	0	0	Dig	1.0 gm	6	
28 A D P† 34	Staphylococcus aureus, Bacillus influenzae	R L	0	0	0	0	Stroph	0.7 mg	8	
29 G E‡ 7	Pneumococcus IV Bacillus influenzae	Dif bilat	0	0	0	0	Stroph	0.5 mg	21	

\* Died

† Patient had mitral stenosis

‡ Died, strophanthin given late

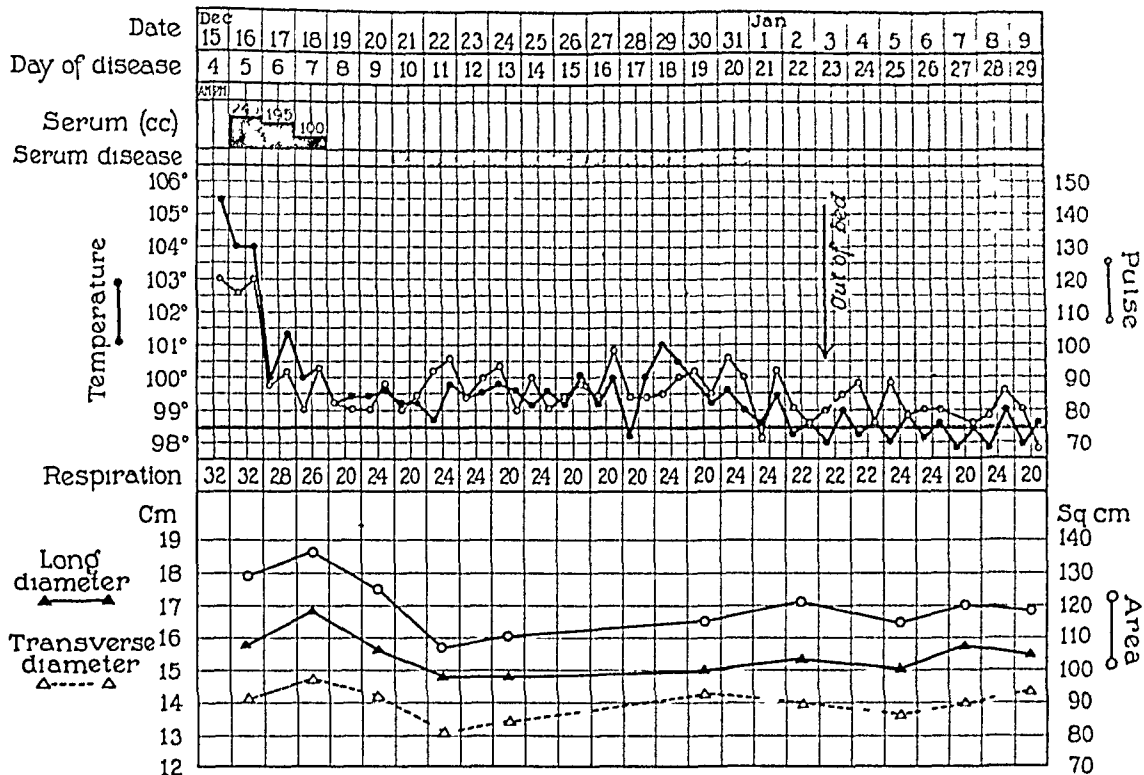


Fig 9 (Case 2) —Clinical chart and cardiac measurements of a woman, aged 29, with lobal pneumonia of the left lower lobe, pneumococcus, Type I

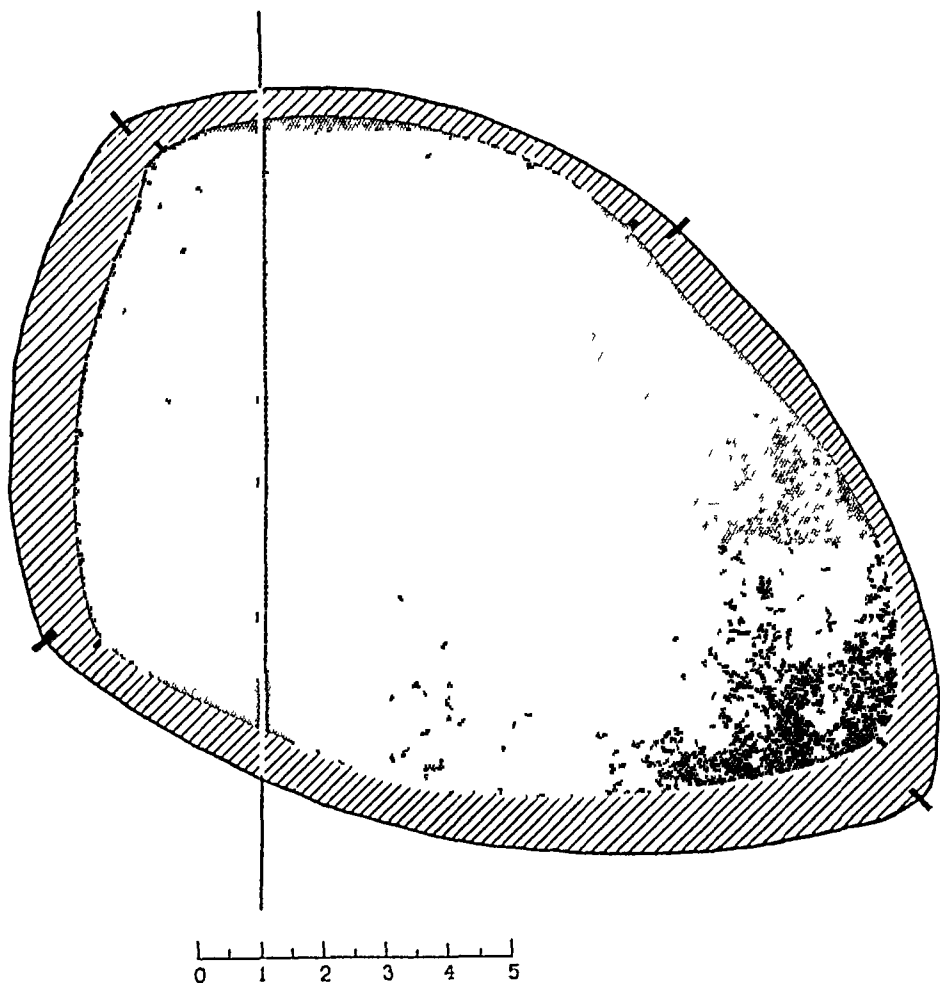


Fig 10 (Case 2) —Silhouettes showing extremes of variation in heart size

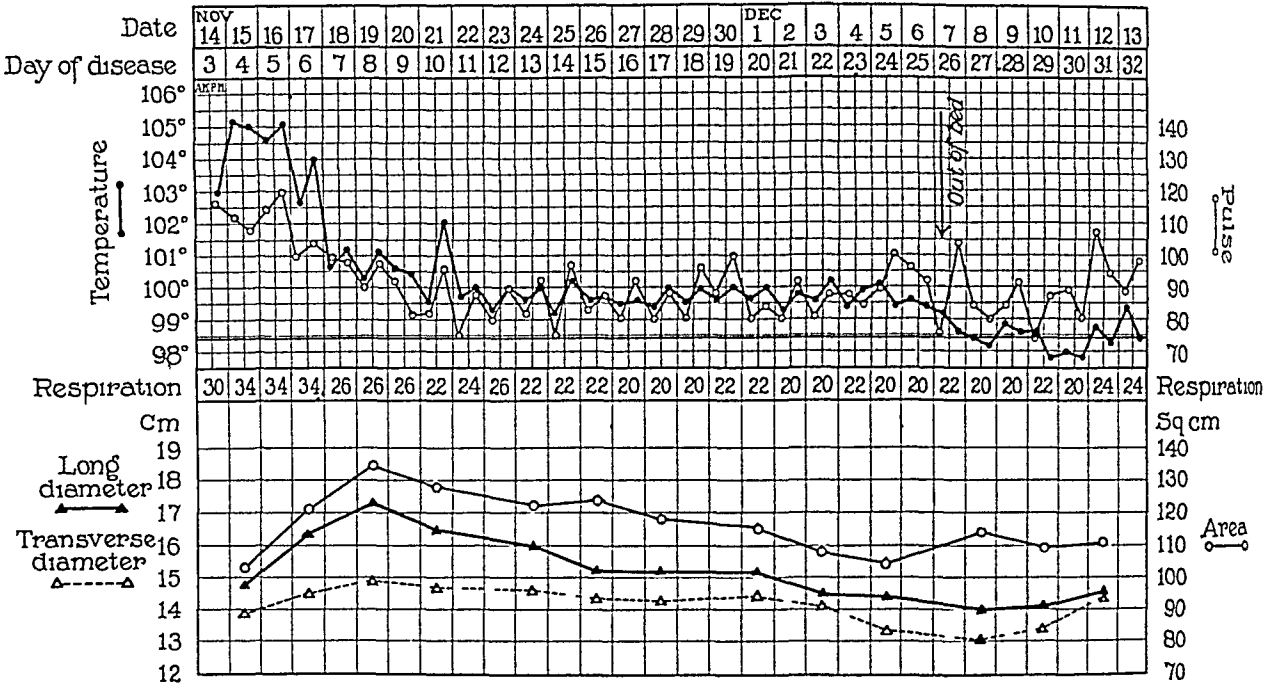


Fig 7 (Case 23) —Clinical chart and cardiac measurements of a woman, aged 55, with bronchopneumonia of the left lower lobe, pneumococcus, Group IV

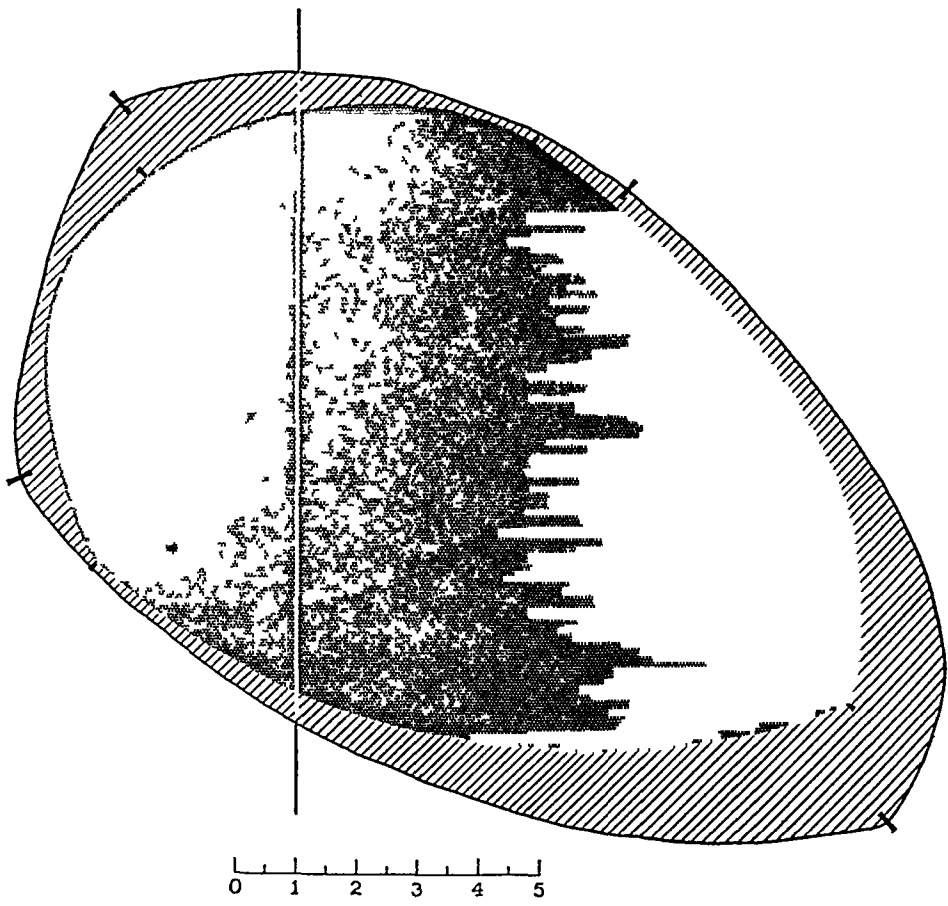


Fig 8 (Case 23) —Silhouettes showing extremes of variation in heart size

of cardiac dilatation in lobar pneumonia (61·9 per cent) than in bronchopneumonia (25 per cent). Aside from structural change, there are present in pneumonia at least three conditions which are concerned in throwing an added burden of work on the heart. These are (1) impairment of the circulation in the pneumonic lung, (2) toxemia, and (3) anoxemia.

(1) *Impairment of the Circulation in the Lung* In a study of injected lungs from patients dying of lobar pneumonia, Kline and Winternitz<sup>7</sup> and, more recently, Gross<sup>8</sup> have demonstrated varying degrees of vascular obliteration, depending in extent on the stage of pulmonary consolidation. In a lung described by Gross, in which the two upper lobes were consolidated, the lower lobe showed tremendous dilatation of the vessels with massive injection. The capillaries appeared to be two or three times their normal caliber, and the entire lobe presented a striking picture of compensatory arterial dilatation. In the upper lobe, there was some preservation of the circulation, but the injected vessels were narrowed. The middle lobe showed general lack of injection, only several large, compressed branches were apparent, and these ended abruptly. Thus, when exudation is at its height, there is almost complete vascular obliteration. With the arterial bed in the lung markedly diminished in area, the pressure in the pulmonary artery is increased, and the right ventricle is obliged to contract against a heightened resistance.<sup>9</sup> In bronchopneumonia this factor is probably of less significance than in lobar pneumonia.

(2) *Toxemia* The heart muscle in pneumonia is fed by blood containing bacterial toxins and perhaps also products of autolysis yielded by the exudate in the lung alveoli. Pertinent experimental evidence on the effect of these poisons on the heart is afforded by the work, on dogs, of Newburgh and Porter<sup>10</sup>. They found that the heart muscle is not functionally impaired in pneumonia, since the pneumonic ventricle beats normally as soon as it is fed with normal blood, that pneumonic blood, suddenly fed to normal heart muscle, lowers its efficiency, lessening the duration and the force of contraction, but that the heart muscle in pneumonia, exposed gradually to the action of the poison, largely adjusts itself to the poisoned food. Clinical observations lend support to these findings.

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7 Kline, B. S., and Winternitz, M. C. Studies Upon Experimental Pneumonia in Rabbits. VIII. Intra Vitam Staining in Experimental Pneumonia and the Circulation in the Pneumonic Lung, *J. Exper. M.* **21** 311, 1915.

8 Gross, L. Preliminary Report on the Reconstruction of the Circulation of the Liver, Placenta and Lung in Health and Disease, *Canad. M. A. J.* **9** 632, 1919.

9 Wiggers, C. J. Circulatory Failure, *J. A. M. A.* **70** 508 (Feb. 23) 1918.

10 Newburgh, L. H., and Porter, W. T. The Heart Muscle in Pneumonia, *J. Exper. M.* **22** 123, 1915.

character to that seen in the latter condition. Evidence of the influence of digitalis is scant, but it tends to support the view that when the drug is given, cardiac dilatation is less likely to occur.

#### DISCUSSION

*Cardiac Dilatation*—The heart is able to adapt itself in remarkable fashion to variations in the demands made on it in the form of mechanical work. The mechanism of this adaptation has been made the subject of particular study by Starling,<sup>4</sup> employing the heart-lung preparation. He found that any increase in the work of the heart, however caused, whether by a rise in the arterial pressure or by a more rapid venous inflow, is attended by a corresponding increase in the volume of the ventricles. And, within physiologic limits, the larger the volume of the heart, the greater is the energy of its contractions as measured by systolic output. The law of the heart is thus the same as the law of muscular tissue in general, that "the energy of contraction, however measured, is a function of the length of the muscle fibre." Up to a physiologic optimum, cardiac dilatation is an adaptive, compensatory mechanism favorable to the maintenance of an adequate circulation. In a healthy person, to accomplish this adaptation may be only a temporary necessity, for the circulation improves as a result of augmented cardiac efficiency, the cardiac tone itself increases, and the heart gradually returns to a normal volume even though doing increased work. But, when the heart is fatigued or diseased, the secondary improvement fails to appear, and the myocardium remains dilated over the period of increased work. If the work is prolonged, dilatation may become permanent, and may even exceed the optimum length of muscle fiber. If this occurs, the muscle must contract at so great a mechanical disadvantage that heart failure ensues.

Anatomic lesions in the heart in pneumonia are, according to a majority of investigators, infrequent and, relatively speaking, insignificant.<sup>5</sup> In the pneumonias associated with influenza in soldiers, Stone,<sup>6</sup> however, reports parenchymatous, fatty and hyaline degeneration or evidence of inflammatory reaction in the heart muscle in 79.3 per cent of the microscopic sections from thirty-four necropsies of cases of lobar pneumonia and in 59.4 per cent of the sections from thirty-seven necropsies of cases of bronchopneumonia. It is of interest to recall, in this connection, the greater frequency, in the present study,

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4 Starling, E. H. *The Linacre Lecture on the Law of the Heart*, Longmans, Green & Co., London, 1918.

5 Cohn, A. E., and Jamieson, R. A. *The Action of Digitalis in Pneumonia*, J. Exper. M. **25** 65, 1917. (This article, on p. 73, contains a review of the literature.)

6 Stone, W. J. *The Heart Muscle Changes in Pneumonia, with Remarks on Digitalis Therapy*, Am. J. M. Sc. **163** 659, 1922.

Another consideration, however, leads to the suggestion that digitalis may be a rationally useful therapeutic measure. Cohn and I<sup>13</sup> have shown, in dogs, that digitalis, in amounts comparable to the therapeutic dose in man, increases the contractile power of the ventricular muscle, and by so doing augments systolic volume output. At a time when the increase in output occurs, there are usually characteristic changes in the T-wave of the electrocardiogram.

From the facts presented in this paper, it is evident that the heart muscle in pneumonia may attempt, by calling on a reserve mechanism, dilatation to augment systolic output. In a relatively large number of the patients who received digitalis, the heart did not increase in size. It, therefore, seems reasonable to infer that when the ventricle is stimulated to increased force of contraction by digitalis, the compensatory mechanism of dilatation, in some instances at least, is not called into play. To that extent, the reserve force of the heart is not encroached on. It is, therefore, logical to suggest the use of early and adequate digitalis therapy in pneumonia, in the belief that it may exert a beneficial effect not only in the presence of auricular fibrillation and flutter, but also when the normal rhythm prevails.

#### SUMMARY

1 A teleroentgenographic study was made of twenty-one cases of lobar pneumonia and eight cases of bronchopneumonia, employing a special technic in making the plates and a new method in completing the outline of the cardiac silhouette.

2 In lobar pneumonia, cardiac dilatation occurred in 61.9 per cent of the cases. Dilatation was less frequently observed in patients who received digitalis (50 per cent) than in those to whom the drug was not given (72.7 per cent).

3 In bronchopneumonia, cardiac dilatation was less frequent than in lobar pneumonia, having been observed in 25 per cent of the cases. The two patients in this group who received digitalis showed no dilatation.

4 The heart muscle in pneumonia may attempt, by lengthening its muscle fibers, to augment systolic output. Digitalis, in therapeutic doses, increases the contractile power of the ventricles. On the basis of these facts, early and adequate digitalis therapy is suggested in pneumonia, in the belief that the drug may exert a beneficial effect, not only in the presence of auricular fibrillation and flutter, but also when the normal rhythm prevails.

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<sup>13</sup> Cohn, A. E., and Levy, R. L. The Effect of Therapeutic Doses of Digitalis on the Contraction of Heart Muscle, *Proc. Soc. Exptl. Biol. & Med.* **17**: 160, 1920.



(3) Anoxemia High arterial unsaturation, with its accompanying clinical manifestation, cyanosis, is a frequent occurrence in both lobar and bronchopneumonia, due, in large measure, according to Stadie,<sup>11</sup> to an impairment in the function of the respiratory surface of the lungs. The greater the lung involvement, the greater is the anoxemia. Especially is this so when the pneumonic process extends throughout the lungs, as is the case when there are many patches of bronchopneumonia, with accompanying bronchitis and edema. That the circulation as a whole may suffer from oxygen want is evident from Stadie's observation that, after administration of oxygen in 60 per cent concentration in a closed chamber, to a moribund and pulseless patient, the heart rate fell from 160 to 120, the pulse returned to the radial artery, the color became pink, and there was remarkable clinical improvement.<sup>12</sup> Other, less striking observations support this view. No records of the size of the heart were made in his cases.

It seems clear, then, that for the reasons given, and perhaps others, the heart may be called on to do more than its usual quota of mechanical work in pneumonia, and that, in certain instances, it responds to the increased demands made on it by dilatation, with resultant lengthening of its muscle fibers. Whether the physiologic optimum of lengthening is ever exceeded, remains an open question. Certainly the signs of heart failure, in the ordinary sense, are conspicuous by their absence. The venous pressure, taken by the method of Hooker, was, moreover, in a number of our cases, within normal limits. The mechanism of adaptation, as has been pointed out, is a gradual one, sometimes reaching its maximum after the height of the disease has been passed. The return of the heart to a smaller and constant volume is likewise a gradual process, and, in that sense, may be regarded as indicating recovery from a functional injury.

*The Therapeutic Use of Digitalis*—Clinicians are agreed that when auricular fibrillation or flutter occurs in the course of pneumonia, the prompt exhibition of digitalis in adequate doses exerts not merely a beneficial effect but is at times responsible for the saving of life. In the presence of normal (sinus) rhythm, there is still doubt as to its value. Cohn and Jamieson<sup>5</sup> have pointed out that in patients with pneumonia the usual digitalis effects on auriculoventricular conduction and on the T-wave of the electrocardiogram may be obtained, and that whatever beneficial action the drug has on the function of the normally beating, nonfebrile heart may also be expected from its use in pneumonia.

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11 Stadie, W. C. The Oxygen of the Arterial and Venous Blood in Pneumonia and Its Relation to Cyanosis, *J. Exper. M.* **30** 215, 1919.

12 Stadie, W. C. The Treatment of Anoxemia in Pneumonia in an Oxygen Chamber, *J. Exper. M.* **25** 337, 1922.

TABLE 9—Findings in a Case of Lobar Pneumonia \*

Date	Day of Dis- case	Roentgenographic Data							Clinical Data			
		Plate No	Maxi- mum Right, Cm	Maxi- mum Left, Cm	Transverse Diam- eter Cm	Long Diam- eter Cm	Area, Sq Cm	Angle, De- grees	Serum, Oc	Serum, Dis- ease	Maxi- mum Temper- ature	Maxi- mum Pulse
4/28/21	4								90		106.0	115
4/29/21	5	5423	5.0	11.1	16.1	15.5	144	22	200		106.8	122
4/30/21	6								100		101.6	85
5/ 2/21	8	5433	5.1	11.1	16.2	16.2	141	24			99.5	80
5/ 4/21	10	5453	5.6	9.9	15.5	15.3	131	26			99.0	72
5/ 6/21	12	5467	5.5	10.1	15.6	15.2	130	26			98.6	76
5/ 9/21	15	5476	5.4	10.3	15.7	15.3	129	25		+	99.4	68
5/11/21	17	5483	5.2	10.6	15.8	15.3	132	23		+	98.8	72
5/13/21	19	5491	5.5	10.1	15.6	15.4	131	24			99.2	74
5/16/21	22	5500	4.6	11.1	15.7	15.4	133	22			98.8	68
5/18/21	24	5512	5.3	10.5	15.8	15.3	129	21			99.4	68
5/20/21	26	5518	5.4	10.4	15.8	15.3	131	23			99.2	72

\* Case 4, H. D., a man, aged 39 years, had pneumonia of the left lower lobe. Pneumo- coccus, Type I, was present. The patient recovered.

TABLE 10—Findings in a Case of Lobar Pneumonia \*

Date	Day of Dis- case	Roentgenographic Data							Clinical Data			
		Plate No	Maxi- mum Right, Cm	Maxi- mum Left, Cm	Transverse Diam- eter Cm	Long Diam- eter Cm	Area, Sq Cm	Angle, De- grees	Serum, Oc	Serum, Dis- ease	Maxi- mum Temper- ature	Maxi- mum Pulse
11/24/19	4										105.0	134
11/25/19	5	4000	5.0	8.7	13.7	14.3	114	37	100		105.6	132
11/26/19	6	4009	4.7	9.2	13.9	14.4	112	35	105		106.0	130
11/28/19	8	4015	4.7	9.5	14.2	14.8	125	39			99.4	68
11/30/19	10									+	99.0	60
12/ 1/19	11	4029	4.6	10.0	14.6	14.8	127	35			99.1	54
12/ 3/19	13	4040	4.8	9.3	14.1	14.5	120	36			99.6	72
12/ 5/19	15	4060	3.9	10.1	14.0	13.7	114	30			99.4	74
12/ 6/19	16									+	99.0	68
12/ 8/19	18	4068	4.9	8.9	13.8	14.2	113	34			99.0	70
12/10/19	20	4082	4.4	9.8	14.2	14.7	120	33			99.1	72
12/12/19	22	4091	5.1	9.2	14.3	15.0	128	38			99.2	64
12/15/19	25	4099	4.3	10.2	14.5	14.7	125	33			99.4	72
2/ 7/21Returned	4991		4.9	9.1	14.0	14.1	115	36				

\* Case 5, P. K., a man, aged 19 years, had pneumonia of the left lower lobe. Pneumo- coccus, Type I, and B. Influenzae were present. The patient recovered.

TABLE 11—Findings in a Case of Lobar Pneumonia \*

Date	Day of Dis- case	Roentgenographic Data							Clinical Data			
		Plate No	Maxi- mum Right, Cm	Maxi- mum Left, Cm	Transverse Diam- eter Cm	Long Diam- eter Cm	Area, Sq Cm	Angle, De- grees	Serum, Oc	Serum, Dis- ease	Maxi- mum Temper- ature	Maxi- mum Pulse
12/ 3/19	1								75		101.8	124
12/ 4/19	5	4050	5.3	10.4	15.7	16.5	144	36	195		105.0	112
12/ 5/19	6								290		103.0	102
12/ 6/19	7								265		101.6	96
12/ 8/19	9	4071	4.0	11.3	15.3	16.8	132	32		+	100.8	86
12/10/19	11	4084	4.9	10.1	15.0	15.9	131	36		+	101.6	88
12/12/19	13	4095	4.3	10.6	14.9	15.4	128	31		+	102.4	100
12/15/19	16	4101	4.4	10.8	15.2	16.0	131	32			99.6	90
12/17/19	18	4110	4.9	10.3	15.2	16.4	136	34			99.4	76
12/19/19	20	4116	4.9	10.0	14.9	15.6	120	34			99.6	78
12/22/19	23	4123	4.1	10.8	14.9	16.1	130	35			99.2	88
12/24/19	25	4135	4.9	11.1	15.0	15.9	133	33			99.6	88
12/30/19	31	4143	4.8	10.2	15.0	16.4	138	36			99.5	88
2/ 7/21Returned	4990		4.8	10.5	15.3	15.6	141	34				

\* Case 6, L. M., a man, aged 21 years, had pneumonia of the right and left lower lobes. Pneumococcus, Type I, and B. Influenzae were present. The patient recovered.

## APPENDIX

TABLE 6—Findings in a Case of Lobal Pneumonia\*

Date	Day of Disease	Roentgenographic Data							Clinical Data			
		Plate No	Maximum Right, Cm	Maximum Left, Cm	Transverse Diameter, Cm	Long Diameter, Cm	Area, Sq Cm	Angle, Degrees	Serum, C c	Serum, Dis-ease	Maximum Temperature	Maximum Pulse
1/ 2/20	5	4151	2 8	9 2	12 0	13 3	89	25	190		104 5	128
1/ 5/20	8	4158	2 9	9 0	11 9	13 5	93	36			100 1	80
1/ 7/20	10	4164	2 4	9 3	11 7	12 6	84	29			100 1	80
1/ 9/20	12	4171	2 9	8 1	11 0	12 3	81	32			100 0	84
1/14/20	17	4184	3 2	8 3	11 5	12 4	82	31			99 0	86
1/16/20	19	4193	3 2	8 3	11 5	12 7	83	32			99 6	84
1/19/20	22	4204	3 3	8 7	12 0	13 3	88	33			99 6	84
1/21/20	24	4215	3 5	7 8	11 3	12 7	80	33			99 3	96
1/23/20	26	4227	3 6	8 4	12 0	13 0	86	31		+	99 3	80
1/26/20	29	4237	3 3	8 4	11 7	13 0	82	33		+	99 4	85
2/ 8/21	Returned	4997	4 0	8 4	12 8	13 1	85	28				86

\* Case 1, F M, a man, aged 52 years, had pneumonia of the left lower lobe. Pneumococcus, Type I, and B influenzae were present. The patient recovered.

TABLE 7—Findings in a Case of Lobal Pneumonia\*

Date	Day of Disease	Roentgenographic Data							Clinical Data			
		Plate No	Maximum Right, Cm	Maximum Left, Cm	Transverse Diameter, Cm	Long Diameter, Cm	Area, Sq Cm	Angle, Degrees	Serum, C c	Serum, Dis-ease	Maximum Temperature	Maximum Pulse
12/15/19	4										105 4	124
12/16/19	5	4104	4 5	9 6	14 1	15 8	129	40	245		105 2	128
12/17/19	6								195		103 0	108
12/18/19	7	4113	4 0	10 7	14 7	16 8	136	40	100		101 5	100
12/20/19	9	4120	3 6	10 6	14 2	15 6	125	39			99 6	88
12/21/19	10									+	99 2	88
12/22/19	11	4122	2 9	10 2	13 1	14 8	107	40		+	99 7	96
12/24/19	13	4132	3 0	10 4	13 4	14 8	110	38		+	99 7	93
12/30/19	19	4140	3 0	11 2	14 2	15 0	115	33		+	99 8	92
1/ 2/20	22	4149	4 2	9 7	13 9	15 3	120	37			99 0	90
1/ 3/20	23										99 6	84
1/ 5/20	25	4155	3 9	9 8	13 7	15 0	115	39			99 6	88
1/ 7/20	27	4163	3 5	10 4	13 9	15 7	120	41			98 4	88
1/ 9/20	29	4168	4 4	9 9	14 3	15 4	118	38			98 6	90
2/ 4/21	Returned	4978	5 0	8 3	13 3	14 3	113	41				

\* Case 2, M F, a woman, aged 29 years, had pneumonia of the left lower lobe. Pneumococcus, Type I, was present. The patient recovered.

TABLE 8—Findings in a Case of Lobal Pneumonia\*

Date	Day of Disease	Roentgenographic Data							Clinical Data			
		Plate No	Maximum Right, Cm	Maximum Left, Cm	Transverse Diameter, Cm	Long Diameter, Cm	Area, Sq Cm	Angle, Degrees	Serum, C c	Serum, Dis-ease	Maximum Temperature	Maximum Pulse
11/25/19	4										103 8	120
11/26/19	5	4008	4 5	11 3	15 8	16 0	145	32	300		103 8	120
11/27/19	6								195		102 8	108
11/28/19	7	4014	4 7	10 7	15 4	16 0	141	38			100 2	80
12/ 1/19	10	4028	3 8	12 7	16 5	16 7	147	33			99 2	76
12/ 2/19	11									+	99 2	78
12/ 3/19	12	4042	4 1	11 3	15 4	15 1	123	32		+	99 6	99
12/ 5/19	14	4061	4 1	11 4	15 6	14 8	124	34		+	99 0	78
12/ 8/19	17	4069	3 4	11 9	15 3	14 8	124	29		+	99 4	72
12/10/19	19	4083	4 5	11 1	15 6	15 7		28		+	99 4	86
12/12/19	21	4090	4 4	11 1	15 5	15 3	126	34			99 2	78
12/15/19	24	4100	4 2	11 3	15 5	15 8	132	34			99 0	78
2/ 2/21	Returned	4963	5 6	9 0	14 6	15 5	138	44				

\* Case 3, S P, a man, aged 36 years, had pneumonia of the left lower lobe. Pneumococcus, Type I, and B influenzae were present. The patient recovered.

TABLE 15—Findings in a Case of Lobar Pneumonia \*

Date	Day of Disease	Plate No	Roentgenographic Data						Clinical Data	
			Maxi mum Right, Cm	Maxi mum Left, Cm	Transverse Diam eter, Cm	Long Diam eter, Cm	Area, Sq Cm	Angle, Degrees	Maxi mum Tempera- ture	Maxi mum Pulse
3/28/21	5								105.0	126
3/29/21	6	5270	17	8.6	13.3	14.1	105	39	104.1	108
3/31/21	8	5280	16	8.8	13.1	11.3	106	40	99.2	72
4/ 2/21	10	5291	19	9.7	13.1	14.3	101	36	99.2	80
4/ 5/21	13	5307	16	8.3	12.9	13.7	100	38	99.6	76
4/ 7/21	15	5311	14	8.1	12.8	13.5	101	38	99.4	72
4/ 9/21	17	5319	19	9.2	13.1	13.8	101	36	99.9	80
4/11/21	19	5326	11	9.1	13.2	11.0	108	41	100.0	86
4/13/21	21	5336	12	8.4	12.6	13.5	101	39	100.1	74
4/15/21	23	5352	15	8.0	12.5	14.1	101	42	100.0	88
4/18/21	26	5364	12	8.9	13.1	11.2	101	38	99.6	84
4/20/21	28	5381	13	8.5	12.8	11.0	101	37	100.0	90
4/22/21	30	5390	13	8.7	13.0	11.1	101	36	100.0	80
4/25/21	33	5408	17	8.2	12.9	11.3	101	41	100.1	92
4/27/21	35	5405	12	8.3	12.5	11.9	101	39	99.8	88

\* Case 10, J. S., a man, aged 28, had pneumonia of the left lower lobe. Pneumococcus, Group IV, was present. The patient recovered.

TABLE 16—Findings in a Case of Lobar Pneumonia \*

Date	Day of Disease	Plate No	Roentgenographic Data						Clinical Data	
			Maxi- mum Right, Cm	Maxi- mum Left, Cm	Transverse Diam- eter, Cm	Long Diam- eter, Cm	Area, Sq Cm	Angle, Degrees	Maxi- mum Temper- ature	Maxi- mum Pulse
2/14/21	6								101.2	116
2/15/21	7	5037	13.5	8.8	12.1	13.1	79	27	101.0	100
2/17/21	9	5051	18	8.8	12.6	11.3	82	27	98.8	84
2/18/21	10	5059	12	8.1	12.6	13.2	81	26	98.8	81
2/21/21	13	5072	10	8.5	12.5	13.0	81	25	99.6	80
2/22/21	14								99.0	86
2/23/21	15	5080	17	8.7	12.1	12.7	77	21	99.6	81
2/25/21	17	5087	19	8.2	12.1	12.5	76	26	99.6	96
2/28/21	20	5101	13.3	8.8	12.1	12.4	77	25	99.1	160

Case 11, S. B., a youth aged 13 years, had pneumonia of the right upper lobe. Pneumococcus, Type I, and B influenzae were present. The patient recovered.

TABLE 17—Findings in a Case of Lobar Pneumonia \*

Date	Day of Disease	Plate No	Roentgenographic Data						Clinical Data				
			Maxi- mum Right, Cm	Maxi- mum Left, Cm	Trans- verse Diam- eter, Cm	Long Diam- eter, Cm	Area, Sq Cm	Angle, Degrees	Serum Dis- ease	Serum Dis- ease	Dig- tan, Gm	Maxi- mum Temper- ature	Maxi- mum Pulse
2/ 6/21	1											101.4	120
2/ 7/21	5	5001	5.1	9.0	14.1	15.1	120	40			0.2	106.7	150
2/ 8/21	6										0.1	103.1	128
2/11/21	9	5021	5.3	8.6	13.0	15.3	119	41				99.3	68
2/14/21	12	5031	5.2	8.1	11.6	15.0	110	39	+			99.2	92
2/16/21	14	5040	4.8	8.9	13.7	15.2	114	40	+			99.4	109
2/19/21	17	5062	4.1	9.6	11.0	15.6	111	38	+			99.3	82
2/21/21	19	5070	4.8	9.1	14.2	15.6	120	35	+			99.0	84
2/22/21	21	5082	5.6	8.1	13.7	14.6	109	38	+			99.8	91
2/25/21	24	5088	5.5	8.6	14.1	15.5	121	38				98.5	88
2/28/21	27	5099	6.1	7.6	13.7	15.1	110	37				99.3	78
3/ 3/21	29	5126	5.3	8.3	13.6	15.0	108	38				99.0	96
3/ 7/21	33	5141	5.3	8.2	13.5	15.0	113	35				99.6	80

\* Case 12, T. O., a man, aged 20 years, had pneumonia of the right lower lobe. Pneumococcus, Type I, was present. The patient recovered.

TABLE 12—Findings in a Case of Lobar Pneumonia

Date	Day of Disease	Plate No	Roentgenographic Data						Clinical Data	
			Maxi mum Right, Cm	Maxi mum Left, Cm	Transverse Diam eter, Cm	Long Diam eter, Cm	Area, Sq Cm	Angle, Degrees	Maxi mum Temper ature	Maxi mum Pulse
3/ 9/21	6								103.9	100
3/10/21	7	5155	4.0	9.7	13.7	14.1	109	36	101.6	92
3/12/21	9	5167	4.6	8.5	13.1	13.9	103	40	100.0	88
3/14/21	11	5169	5.7	7.5	13.2	13.4	101	38	100.0	72
3/16/21	13	5185	5.4	7.5	12.9	13.1	100	39	100.1	72
3/18/21	15	5196	5.6	7.4	13.0	13.3	101	38	99.6	72
3/21/21	18	5211	5.5	8.0	13.5	13.7	106	33	99.4	84
3/23/21	20	5230	5.5	8.5	14.0	14.1	110	35	99.4	72
3/25/21	22	5249	5.0	8.9	13.9	14.1	112	34	99.6	84
3/28/21	25	5262	5.5	8.4	13.9	14.6	115	33	99.2	76
3/30/21	27	5275	4.8	9.0	13.8	14.3	113	33	99.4	72

\* Case 7, F. T., a man, aged 29 years, had pneumonia of the right lower lobe. Pneumococcus, Group IV, and B influenzae were present. The patient recovered.

TABLE 13—Findings in a Case of Lobar Pneumonia\*

Date	Day of Disease	Plate No	Roentgenographic Data						Clinical Data	
			Maxi mum Right, Cm	Maxi mum Left, Cm	Transverse Diam eter, Cm	Long Diam eter, Cm	Area, Sq Cm	Angle, Degrees	Maxi mum Temper ature	Maxi mum Pulse
12/ 4/19	5								103.8	98
12/ 5/19	6	4059	4.2	11.6	15.8	16.5	134	33	103.0	96
12/ 8/19	9	4070	3.7	11.0	14.7	16.8	127	37	99.5	72
12/10/19	11	4081	4.4	9.1	13.5	15.9	117	39	99.1	83
12/12/19	13	4092	5.0	8.7	13.7	15.8	113	37	99.3	80
12/15/19	16	4098	5.2	8.9	14.1	15.5	114	35	99.0	78
12/17/19	18	4109	4.8	9.5	14.3	15.9	123	33	99.0	84
12/18/19	19								99.0	78
12/19/19	20	4118	4.5	10.0	14.6	15.8	119	28	99.0	84
12/22/19	23	4125	4.5	9.4	13.9	15.4	120	34	99.0	80
12/24/19	25	4134	3.8	10.5	14.3	15.6	122	32	99.2	82
12/30/19	31	4144	3.8	10.8	14.7	15.7	121	27	99.2	80

\* Case 8, T. M., a man, aged 47 years, had pneumonia of the right lower lobe. Pneumococcus, Type IIA, was present. The patient recovered.

TABLE 14—Findings in a Case of Lobar Pneumonia\*

Date	Day of Disease	Plate No	Roentgenographic Data						Clinical Data	
			Maxi mum Right, Cm	Maxi mum Left, Cm	Transverse Diam eter, Cm	Long Diam eter, Cm	Area, Sq Cm	Angle, Degrees	Maxi mum Temper ature	Maxi mum Pulse
4/12/21	6								104.1	148
4/13/21	7	5338	3.4	12.1	15.5	15.6	127	26	102.9	102
4/18/21	12	5336	3.7	12.0	15.7	15.9	130	25	99.9	72
4/20/21	14	5382	4.4	10.8	15.2	15.6	120	29	99.4	82
4/22/21	16	5391	4.5	11.1	15.6	15.7	126	26	99.9	80
4/25/21	18	5399	5.3	10.3	15.6	15.8	123	28	99.6	84
4/27/21	20	5406	5.5	10.1	15.6	16.0	125	30	99.2	87
4/29/21	22	5417	5.2	9.9	15.1	15.5	118	28	99.4	82
5/ 2/21	26	5431	5.6	9.9	15.5	15.5	122	26	100.0	88
5/ 4/21	28	5451	5.5	9.9	15.4	15.8	128	29	99.6	86
5/ 6/21	30	5464	5.5	9.8	15.3	15.6	124	32	100.0	80
5/ 9/21	33	5474	5.4	10.5	15.9	16.0	130	30	100.0	80

\* Case 9, J. K., a youth, aged 18 years, had pneumonia of the right and left lower lobes. Pneumococcus Type II was present. The patient recovered.

TABLE 21—Findings in a Case of Lobar Pneumonia<sup>a</sup>

Date	Day of Disease	Roentgenographic Data							Clinical Data		
		Plate No	Maximum Right, Cm	Maximum Left, Cm	Transverse Diam eter Cm	Long Diam eter Cm	Area, Sq Cm	Angle, Degrees	Digitan, Gm	Maximum Temperature	Maximum Pulse
10/12/21	3									104.4	98
10/13/21	4	5681	5.3	9.8	15.1	15.0	108	27	1.0	102.6	96
10/14/21	5								0.5	103.2	96
10/15/21	6	5689	5.0	9.7	14.7	14.4	107	26		102.4	88
10/18/21	9	5695	5.6	10.1	15.7	15.1	115	24		100.2	76
10/20/21	11	5704	5.0	11.1	16.1	15.4	115	22		99.8	60
10/22/21	13	5714	5.5	10.7	16.2	15.8	119	23		99.6	68
10/24/21	15	5719	4.9	11.0	15.9	15.7	114	24		99.7	68
10/26/21	17	5728	4.5	11.3	15.8	15.5	114	21		99.6	74

<sup>a</sup> Case 16, F. L., a man, aged 32 years, had pneumonia of the left lower lobe and chronic heroin poisoning. Pneumococcus, Group IV, was present. The patient recovered from pneumonia but the second condition was unimproved.

TABLE 22—Findings in a Case of Lobar Pneumonia<sup>a</sup>

Date	Day of Disease	Roentgenographic Data							Clinical Data				
		Plate No	Maximum Right, Cm	Maximum Left, Cm	Trans Diameter, Cm	Long Diameter, Cm	Area, Sq Cm	Angle Degrees	Serum C c	Serum Disease	Digitan, Gm	Maximum Temperature	Maximum Pulse
2/23/21	4											104.6	120
2/24/21	5	5085	5.1	7.5	12.6	12.9	99	32	90		0.3	105.0	112
2/25/21	6								180		0.7	104.2	104
2/26/21	7	5097	5.4	7.2	12.6	13.0	100	34			0.5	100.6	98
3/ 1/21	10	5112	5.0	7.1	12.1	12.7	97	26				100.3	80
3/ 2/21	12	5127	5.0	6.7	11.7	12.3	94	38				99.9	92
3/ 4/21	13									+		100.4	92
3/ 5/21	14	5137	5.5	6.5	12.0	12.5	95	37		+		101.9	95
3/ 7/21	16	5143	5.4	6.6	12.0	12.2	96	34				100.6	100
3/ 9/21	18	5152	5.5	6.3	11.8	12.4	95	37				100.6	88
3/11/21	20	5159	5.5	6.5	12.0	12.6	99	38				99.3	88
3/14/21	23	5170	5.2	7.0	12.2	12.9	100	35				100.0	84
3/16/21	25	5186	5.4	6.6	12.0	12.3	96	37				100.0	92
3/18/21	27	5195	5.4	6.9	12.3	12.7	96	34				99.2	90
3/21/21	30	5212	5.8	6.2	12.0	12.8	100	42				99.6	88
3/23/21	32	5231	5.2	6.7	11.9	13.0	101	39				100.0	90

<sup>a</sup> Case 17, V. P., a man, aged 26 years, had pneumonia of the right lower lobe and otitis media of the left ear. Pneumococcus, Type I, was recovered from the sputum, hemolytic streptococci and staphylococci were present in the discharge from the ear. The patient recovered.

TABLE 23—Findings in a Case of Lobar Pneumonia<sup>a</sup>

Date	Day of Disease	Roentgenographic Data						Clinical Data					
		Plate No	Maxi mum Right, Cm	Maxi mum Left, Cm	Trans Diam eter, Cm	Long Diam- eter, Cm	Area, Sq Cm	Angle, De grees	Serum C c	Serum Dis- ease	Digi- tan, Gm	Maxi- mum Temper- ature	Maxi mum Pulse
1/ 4/22	2										0.8	104.0	120
1/ 5/22	3	5985	5.6	7.7	13.3	13.9	100	39	100			105.3	128
1/ 6/22	4	6006	5.5	8.0	13.5	14.2	100	44			0.1	101.4	118
1/ 9/22	7	6013	5.0	7.6	12.6	14.0	106	42				99.6	92
1/11/22	9	6035	4.7	7.6	12.3	13.8	98	40		+		99.4	80
1/14/22	12	6042	4.2	8.1	12.6	13.7	101	37				99.1	88
1/16/22	14	6052	3.6	9.1	12.7	14.1	103	34				99.8	78
1/18/22	16	6068	4.0	8.0	12.0	13.9	99	38				99.1	92
1/20/22	18	6082	4.2	8.5	12.7	13.8	100	38				99.4	80
1/23/22	21	6093	3.6	9.3	12.9	13.9	101	37				99.4	80
1/25/22	23	6109	4.9	8.1	13.3	14.0	104	35				99.2	88

<sup>a</sup> Case 18, M. L., a woman, aged 34, had pneumonia of the left lower lobe. Pneumococcus, Type I, and B influenzae were present. The patient recovered.

† Serum disease began on the ninth day and continued through the eleventh day.

TABLE 18—Findings in a Case of Lobar Pneumonia \*

Date	Day of Disease	Roentgenographic Data						Clinical Data					
		Plate No	Maximum Right, Cm	Maximum Left, Cm	Trans Diam eter, Cm	Long Diam eter, Cm	Area, Sq Cm	Angle De- grees	Serum, C c	Serum, Dis- ease	Digi tan, Gm	Maxi mum Temper ature	Maxi mum Pulse
3/22/21	4	5225	4 1	11 7	15 8	17 4	138	35	180		0 4	104 4	106
3/23/21	5								90		0 4	102 6	92
3/24/21	6	5243	4 9	11 0	15 9	17 5	141	34				100 6	66
3/26/21	8	5257	5 1	10 3	15 4	17 5	139	39				99 7	80
3/28/21	10	5263	4 8	10 9	15 7	17 0	139	33		+		99 4	60
3/30/21	12	5272	4 4	10 2	14 6	15 9	119	32		+		101 6	92
4/ 1/21	14	5286	4 6	10 1	14 7	16 2	124	35		+		99 2	80
4/ 4/21	17	5298	4 9	10 1	15 0	16 5	127	33				99 4	76
4/ 6/21	19	5310	4 7	10 7	15 2	16 3	129	30				99 2	64
4/ 8/21	21	5317	4 5	10 4	14 9	16 0	122	30				99 1	84
4/11/21	24	5327	4 7	10 8	15 5	16 8	124	32				99 1	82
4/13/21	26	5337	4 2	11 8	16 0	16 7	128	28				99 0	84

\* Case 13, P. O'M., a man, aged 25 years, had pneumonia of the right upper, middle and lower lobes. Pneumococcus, Type I, was present. The patient recovered.

TABLE 19—Findings in a Case of Lobar Pneumonia \*

Date	Day of Disease	Roentgenographic Data						Clinical Data					
		Plate No	Maximum Right, Cm	Maximum Left, Cm	Trans Diam eter, Cm	Long Diam eter, Cm	Area, Sq Cm	Angle De-grees	Serum, C c	Serum Dis ease	Digi-tan, Gm	Maxi-mum Temper-ature	Maxi-mum Pulse
11/11/21	4										1 0	104 0	112
11/12/21	5	5798	5 5	8 3	13 8	15 0	110	39	200		0 5	103 6	96
11/13/21	6								200			102 0	100
11/14/21	7	5800	6 0	7 3	13 3	14 5	106	39	100			101 2	108
11/16/21	9	5810	6 1	7 9	14 0	14 8	112	36				101 2	82
11/18/21	11	5816	5 6	7 8	13 4	14 6	109	39				100 8	92
11/19/21	12											102 6	96
11/22/21	15	5824	5 8	7 2	13 0	14 4	103	39		+		102 4	104
11/23/21	16	5828	5 4	8 5	13 9	15 4	115	39		+		102 8	116
11/25/21	18	5833	5 4	8 7	14 1	15 5	116	38		+		103 5	120
11/28/21	21	5839	5 7	8 4	14 1	15 9	118	41				103 0	120
11/30/21	23	5853	5 1	8 9	14 0	15 9	117	39				101 8	102
12/13/21	36	5907	5 3	9 1	14 4	15 3	113	35				99 4	90
12/15/21	38	5913	5 9	8 8	14 7	15 8	114	35				99 1	82
12/19/21	42	5933	4 9	9 2	14 1	15 3	107	35				99 6	88
12/21/21	44	5938	5 1	8 4	13 5	15 2	103	37				100 0	84

\* Case 14, E. D., a man, aged 39 years, had pneumonia of the left lower and right upper lobes. Pneumococcus, Type I, was present. The patient recovered.

TABLE 20—Findings in a Case of Lobar Pneumonia \*

Date	Day of Disease	Roentgenographic Data						Clinical Data			
		Plate No	Maximum Right, Cm	Maximum Left, Cm	Transverse Diameter Cm	Long Diameter Cm	Area, Sq Cm	Angle, Degrees	Digitan, Gm	Maximum Temperature	Maximum Pulse
11/14/19	3									104.2	118
11/15/19	4	3962	3.8	9.4	13.2	15.5	115	41		104.4	110
11/17/19	6	3966	4.0	9.6	13.6	17.0	136	48	1.0	103.9	127
11/19/19	8								0.5	103.0	133
11/21/19	10	3983	3.7	9.1	12.8	15.9	116	47		101.6	98
11/24/19	13	3994	4.0	7.7	11.7	15.1	107	50		101.4	82
11/26/19	15	4007	3.5	8.0	11.5	14.8	103	48		100.6	80
11/28/19	17	4013	3.2	8.7	11.9	15.4	109	46		100.2	90
12/ 1/19	20	4027	2.9	8.7	11.6	14.7	102	32		100.3	100
12/ 3/19	22	4041	3.0	8.7	11.7	15.0	104	45		100.2	86
12/ 5/19	24	4058	3.1	9.0	12.1	14.9	106	44		100.3	88
12/ 8/19	27	4067	3.5	8.1	11.6	14.9	102	46		100.2	88
12/10/19	29	4078	3.8	7.6	11.4	14.2	99	46		100.0	96
12/12/19	31	4089	3.2	8.2	11.4	14.1	101	45		99.0	83
12/15/19	34	4097	3.7	8.0	11.7	14.2	100	45		98.5	80
12/17/19	36	4107	3.6	7.8	11.4	14.6	101	49		98.0	84
12/20/19	39	4119	3.8	7.7	11.5	14.8	103	48		98.5	80
12/24/19	43	4131	4.0	7.2	11.2	14.8	104	50		98.5	88
2/ 9/21	Returned	5003	4.3	7.6	11.9	13.6	102	45			

\* Case 15, A. T., a man, aged 29 years, had pneumonia of the right upper, middle and lower lobes and of the left lower lobe. Pneumococcus, Type III, was present. The patient recovered.

TABLE 27—Findings in a Case of Bronchopneumonia \*

Date	Day of Disease	Plate No	Roentgenographic Data						Clinical Data	
			Maxi- mum Right, Cm	Maxi- mum Left, Cm	Transverse Diam- eter, Cm	Long Diam- eter, Cm	Area, Sq Cm	Angle, Degrees	Maxi- mum Temper- ature	Maxi- mum Pulse
12/ 3/19	8								103.4	100
12/ 4/19	9	4048	5.4	11.4	16.8	18.0	142	28	102.6	102
12/ 6/19	11	1063	5.4	11.4	16.8	17.9	146	26	101.6	94
12/ 8/19	13	4072	5.3	12.1	17.4	18.4	150	26	101.0	84
12/12/19	17	4093	5.1	11.7	16.8	17.9	143	26	101.0	88
12/15/19	20	4102	4.3	11.9	16.2	17.0	128	24	100.5	88
12/17/19	22	4111	5.5	11.7	17.2	17.7	139	18	100.6	80
12/19/19	24	4117	4.0	13.0	17.0	17.8	138	21	100.7	80
12/22/19	27	4121	4.0	13.3	17.3	18.3	139	21	100.7	80
12/24/19	29	4136	4.3	12.4	16.7	17.3	131	20	98.8	78
12/30/19	35	4142	4.1	12.8	17.2	17.8	137	19	98.6	88
1/ 2/20	38	4150	1.8	12.7	17.5	18.1	135	21	97.8	76
1/ 5/20	41	4157	1.4	12.0	16.4	17.2	137	22	98.6	84
2/ 2/21	Returned	4966	5.7	12.2	17.9	18.7	146	23		

\* Case 22, M. Q., a man, aged 39 years, had diffuse bilateral bronchopneumonia. Pneumococcus, Group IV, and B. influenzae were present. The patient recovered.

TABLE 28—Findings in a Case of Bronchopneumonia \*

Date	Day of Disease	Plate No	Roentgenographic Data						Clinical Data	
			Maxi- mum Right, Cm	Maxi- mum Left, Cm	Transverse Diam- eter, Cm	Long Diam- eter, Cm	Area, Sq Cm	Angle, Degrees	Maxi- mum Temper- ature	Maxi- mum Pulse
11/14/19	3								103.0	116
11/15/19	4	3959	3.7	10.2	13.9	14.8	103	39	107.4	112
11/17/19	6	3965	4.0	10.5	14.5	16.4	121	41	104.1	110
11/19/19	8	3976	4.6	10.3	14.9	17.3	135	42	101.0	98
11/21/19	10	3980	4.1	10.6	14.7	16.5	128	41	102.0	96
11/24/19	13	3993	4.1	10.5	14.6	16.0	122	39	100.3	92
11/26/19	15	4005	3.8	10.6	14.1	15.2	124	37	100.5	88
11/28/19	17	4015	3.6	10.7	14.3	15.2	118	37	100.4	88
12/ 1/19	20	4025	3.1	11.0	14.4	15.2	115	35	100.0	84
12/ 3/19	22	4039	4.0	10.1	14.1	14.5	108	38	100.6	96
12/ 5/19	24	4057	4.1	9.2	13.3	14.1	101	37	100.2	100
12/ 8/19	27	4065	4.3	8.8	13.1	14.0	114	43	99.0	98
12/10/19	29	4079	3.5	9.9	13.1	14.2	109	37	98.7	100
12/12/19	31	4088	4.0	10.1	14.4	14.5	111	35	98.7	108

\* Case 23, F. S., a woman, aged 55 years, had bronchopneumonia of the left lower lobe. Pneumococcus, Group IV, was present. The patient recovered.

TABLE 29—Findings in a Case of Bronchopneumonia \*

Date	Day of Disease	Plate No	Roentgenographic Data						Clinical Data	
			Maxi- mum Right, Cm	Maxi- mum Left, Cm	Transverse Diam- eter, Cm	Long Diam- eter, Cm	Area, Sq Cm	Angle, Degrees	Maxi- mum Temper- ature	Maxi- mum Pulse
11/18/19	2								101.0	126
11/19/19	3	3972	4.0	8.2	12.2	11.2	106	50	102.4	110
11/21/19	5	3982	4.1	8.0	12.1	13.6	104	47	100.0	84
11/24/19	8	3991	4.9	8.2	12.1	13.5	102	47	100.0	80
11/26/19	10	4003	3.8	8.5	12.3	14.3	102	49	99.4	80
11/27/19	11								100.0	78
11/28/19	12	4016	3.8	8.3	12.1	13.7	101	45	99.6	80
12/ 1/19	15	4026	4.0	8.3	12.3	13.5	103	46	98.6	80
12/ 3/19	17	4037	3.6	8.6	12.2	13.7	100	46	99.3	88
12/ 5/19	19	4056	3.7	8.1	12.1	13.6	98	45	98.6	80
12/ 8/19	22	4066	3.1	8.6	12.0	13.6	100	42	98.8	80

\* Case 24, A. J., a woman, aged 27 years, had bronchopneumonia of the right lower lobe. Pneumococcus, Group IV, was present. The patient recovered.



TABLE 24—Findings in a Case of Lobar Pneumonia \*

Date	Day of Disease	Roentgenographic Data							Clinical Data		
		Plate No	Maximum Right, Cm	Maximum Left, Cm	Transverse Diameter, Cm	Long Diameter, Cm	Area, Sq Cm	Angle, Degrees	Digit in, Gm	Maximum Temperature	Maximum Pulse <sup>a</sup>
10/21/21	2								0.4	105.2	138
10/22/21	3	5716	4.6	8.6	13.2	13.9	108	35	1.0	104.0	136
10/23/21	4								0.4	102.8	116
10/24/21	5	5718	4.3	9.3	13.6	14.2	114	32		101.1	100
10/26/21	7	5727	4.6	8.9	13.5	13.9	113	29		99.1	80
10/28/21	9	5744	5.3	8.3	13.6	13.9	112	30		98.8	76
10/31/21	12	5755	4.9	8.2	13.1	13.3	107	36		99.4	78
11/ 2/21	14	5761	4.6	8.7	13.3	13.7	111	35		99.5	92
11/ 4/21	16	5771	4.7	8.4	13.1	13.4	109	34		99.0	84

\* Case 19, L. W., a youth, aged 16 years, had pneumonia of the right lower lobe. Pneumococcus, Type II, and B influenzae were present. The patient recovered.

TABLE 25—Findings in a Case of Lobar Pneumonia \*

Date	Day of Disease	Roentgenographic Data							Clinical Data		
		Plate No	Maximum Right, Cm	Maximum Left, Cm	Transverse Diameter, Cm	Long Diameter, Cm	Area, Sq Cm	Angle, Degrees	Digit in, Gm	Maximum Temperature	Maximum Pulse
12/27/21	5	5961	4.5	9.1	13.6	14.4	111	33		104.5	106
12/28/21	6								0.4	104.2	98
12/29/21	7								0.5	103.4	84
12/30/21	8	5965	4.9	9.2	14.1	14.3	108	30		99.6	72
1/ 3/22	12	5970	5.2	8.8	14.0	14.9	112	34		98.6	66
1/ 5/22	14	5986	5.2	8.6	13.9	14.5	108	34		99.0	72
1/ 7/22	16	6004	5.1	9.7	14.8	15.2	114	28		98.9	64
1/ 9/22	18	6010	4.8	9.1	13.9	14.4	104	32		99.0	82
1/11/22	20	6033	4.6	9.8	14.4	14.7	111	29		99.4	72
1/14/22	23	6038	5.0	9.3	14.3	14.8	110	31		99.4	74

\* Case 20, A. R., a man, aged 37 years, had pneumonia of the right upper lobe. Pneumococcus, Group IV, was present. The patient recovered.

TABLE 26—Findings in a Case of Lobar Pneumonia \*

Date	Day of Disease	Roentgenographic Data							Clinical Data		
		Plate No	Maximum Right, Cm	Maximum Left, Cm	Transverse Diameter, Cm	Long Diameter, Cm	Area, Sq Cm	Angle, Degrees	Digit in, Gm	Maximum Temperature	Maximum Pulse
1/ 1/22	2								0.6	102.6	116
1/ 2/22	3								0.4	100.0	69
1/ 3/22	4	5971	4.0	10.0	14.0	14.8	114	42		99.5	65
1/ 5/22	6	5987	3.9	10.4	14.3	14.9	118	36		99.4	65
1/ 6/22	7	6005	4.1	10.3	14.4	14.7	116	31		99.4	65
1/ 9/22	10	6011	4.3	9.9	14.2	14.8	113	35		99.0	68
1/11/22	12	6034	4.2	10.3	14.5	15.0	120	33		99.2	76
1/16/22	17	6049	4.1	10.3	14.4	14.7	115	36		98.4	65
1/18/22	19	6064	4.0	10.1	14.1	14.6	116	33		97.4	70

\* Case 21, R. L., a man, aged 34 years, had pneumonia of the left lower lobe. Pneumococcus, Group IV, and B influenzae were present. The patient recovered.

TABLE 34—*Findings of a Case of Bronchopneumonia* \*

Date	Day of Dis- ease	Roentgenographic Data							Clinical Data		
		Plate No	Maxi- mum Right, Cm	Maxi- mum Left, Cm	Transverse Diam- eter Cm	Long Diam- eter Cm	Area, Sq Cm	Angle, De- grees	Stro- phan- thin, Gm	Maxi- mum Temper- ature	Maxi- mum Pulse
11/23/19	7									102.8	124
11/24/19	8	3995	4.1	5.9	10.1	10.9	81	50		104.6	140
11/26/19	10	4006	4.1	5.7	9.8	10.7	77	51		103.3	135
11/28/19	12	4017	4.0	6.1	10.1	10.7	79	49		102.8	138
12/7/19	21								0.2	102.8	170
12/10/19	24								0.3	104.4	176

\* Case 29, G. L., a boy, aged 7 years, had diffuse bilateral bronchopneumonia. Pneumococcus, Group IV, and B influenzae were present. The patient died.

TABLE 30—Findings in a Case of Bronchopneumonia\*

Date	Day of Disease	Plate No	Roentgenographic Data						Clinical Data	
			Maxi- mum Right, Cm	Maxi- mum Left, Cm	Transverse Diam- eter, Cm	Long Diam- eter, Cm	Area, Sq Cm	Angle, Degrees	Maxi- mum Temper- ature	Maxi- mum Pulse
2/ 3/21	5	4976	4 0	8 5	12 5	13 0	101	33	101 0	90
2/ 9/21	11	5005	4 0	8 4	12 4	12 8	97	35	99 2	70
2/11/21	13	5021	4 1	8 1	12 2	12 7	97	30	99 6	94
2/14/21	16	5033	4 0	8 3	12 3	12 8	98	32	98 3	70

\* Case 25, G B, a girl aged 13 years, had bronchopneumonia of the right lower lobe Streptococcus hemolyticus was present The patient recovered

TABLE 31—Findings in a Case of Bronchopneumonia\*

Date	Day of Disease	Plate No	Roentgenographic Data						Clinical Data	
			Maxi- mum Right, Cm	Maxi- mum Left, Cm	Transverse Diam- eter, Cm	Long Diam- eter, Cm	Area, Sq Cm	Angle, Degrees	Maxi- mum Temper- ature	Maxi- mum Pulse
1/ 9/20	7								103 2	100
1/10/20	8	4173	5 2	9 0	14 2	14 5	118	30	102 8	92
1/12/20	10	4177	5 6	8 5	14 1	14 7	113	31	103 5	116
1/14/20	12	4186	5 0	9 2	14 2	14 5	113	30	103 0	120
1/16/20	14	4194	4 9	9 2	14 1	14 5	112	29	102 8	116
1/19/20	17	4205	5 6	7 3	12 9	13 6	105	36	105 8	128

\* Case 26, C G, a man, aged 35, had diffuse bilateral bronchopneumonia Hemolytic streptococcus and B influenzae were present The patient died

TABLE 32—Findings in a Case of Bronchopneumonia\*

Date	Day of Disease	Plate No	Roentgenographic Data						Clinical Data		
			Maxi- mum Right, Cm	Maxi- mum Left, Cm	Transverse Diam- eter, Cm	Long Diam- eter, Cm	Area, Sq Cm	Angle, De- grees	Digi- tan, Gm	Maxi- mum Temper- ature	Maxi- mum Pulse
11/23/21	5									105 3	110
11/24/21	6								0 6	104 9	108
11/25/21	7	5834	4 6	8 3	12 9	14 5	107	43	0 4	105 2	114
11/29/21	11	5847	4 6	8 1	12 7	14 2	106	42		99 0	108
12/ 1/21	13	5865	4 3	9 1	13 4	15 0	109	40		100 4	88
12/ 5/21	17	5876	4 7	8 1	12 8	14 9	106	44		98 5	80
12/ 7/21	19	5880	4 5	8 4	12 9	14 9	106	42		99 4	86
12/ 9/21	21	5891	4 6	8 6	13 2	14 8	109	41		99 4	86
12/12/21	24	5899	4 0	8 8	12 8	14 8	105	43		99 6	88
12/14/21	26	5909	4 6	8 8	13 4	15 1	109	41		99 8	88
12/19/21	31	5932	4 2	8 6	12 8	14 5	104	42		99 2	90
12/21/21	33	5936	4 1	9 1	13 2	14 9	107	40		99 5	94

\* Case 27, M K, a youth, aged 19 years, had bronchopneumonia of the right lower lobe Pneumococcus Group IV, was present The patient recovered

TABLE 33—Findings in a Case of Bronchopneumonia\*

Date	Day of Disease	Plate No	Roentgenographic Data						Clinical Data		
			Maxi- mum Right, Cm	Maxi- mum Left, Cm	Transverse Diam- eter, Cm	Long Diam- eter, Cm	Area, Sq Cm	Angle, De- grees	Stro- phan- thin, Gm	Maxi- mum Temper- ature	Maxi- mum Pulse
1/ 6/20	7	4161	4 4	7 2	11 6	12 9	89	37		104 0	84
1/ 7/20	8	4166	3 7	7 6	11 3	12 9	89	33	0 7	104 2	86
1/ 9/20	10	4172	4 2	7 2	11 4	12 5	85	36		100 5	70
1/12/20	13	4175	4 4	7 3	11 7	13 1	91	36		99 3	66
1/14/20	15	4183	4 3	7 6	11 9	13 0	93	35		98 6	70
1/16/20	17	4191	4 5	7 2	11 7	13 0	90	38		98 6	63
1/19/20	20	4199	4 3	7 2	11 5	12 7	87	35		98 8	72
1/21/20	22	4213	4 1	7 4	11 5	12 8	89	36		98 8	79
1/23/20	23	4226	4 5	7 0	11 5	12 8	89	36		99 3	88

\* Case 28, A D P, a woman, aged 34 years, had bronchopneumonia of the right lower lobe, chronic endocarditis and mitral stenosis Staphylococcus aureus and albus and B influenzae were present The patient recovered

tonsillitis in a community where this disease is prevalent each winter, and also to collect data on the "normal" state of parasitism of the hemolytic streptococcus in a group of people among whom streptococcus disease was not prevalent. It seemed important to find out not only the percentage of healthy persons who were carriers of hemolytic streptococcus, but also to study the type of parasitism from the standpoint of the number and distribution of the organisms in the upper air passages. With these facts recorded, one could later discover whether the cases of clinical streptococcus infection (tonsillitis) were preceded by any change in the number and distribution of the carriers, whether there was any alteration in the type of growth of streptococcus on the mucous membranes, whether such changes if present were a sequel of the disease outbreak and whether the strains obtained from cases were identical with or different from those previously obtained from carriers. The fundamental importance of such data in relation to the definition of epidemic phenomena is obvious.

#### LITERATURE

The literature on the occurrence of the hemolytic streptococcus in the throats of normal people is large and too well known to require detailed review, but in spite of the volume of observations, little has been brought out which is helpful in interpreting epidemiologic phenomena. Reports concern themselves chiefly with the bare incidence of the organisms, the implication being that the percentage of positives depends largely on the technic of isolation employed. Arnold,<sup>5</sup> for example, in a recent summary of the literature, points out that various observers have recovered hemolytic streptococci in from 15 to 100 per cent of "normal" people. Davis<sup>6</sup> found that if repeated pharyngeal cultures were taken from a group of normal students, sooner or later the beta hemolytic streptococcus was recovered. Davis and Pilot,<sup>7</sup> some years ago laid great stress on the presence of the hemolytic streptococcus in the tonsils and suggested that these organs were an important breeding place for strains which might later produce autogenous infection. This idea has been supported by others, and it is well known that the hemolytic streptococcus is less frequently found in the throats of those whose tonsils have been removed (Van Dyke,<sup>8</sup> Tongs<sup>9</sup>). The high incidence of hemolytic streptococcus in the men at certain camps during the war suggested that concentration of people might lead to rapid dissemina-

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5 Arnold, L. *J. Lab. Clin. Med.* **5**: 3, 1920.

6 Davis, D. J. *J. Infect. Dis.* **29**: 524, 1921.

7 Pilot, I., and Davis, D. J. *J. Infect. Dis.* **24**: 386, 1919.

8 Van Dyke, H. B. Hemolytic Streptococci in the Normal Throat After Tonsillectomy, *J. A. M. A.* **74**: 448 (Feb. 14) 1920.

9 Tongs, M. S. Hemolytic Streptococci in the Nose and Throat, *J. A. M. A.* **73**: 1050 (Oct. 4) 1919.

# DEFINITION OF HEMOLYTIC STREPTOCOCCUS PARASITISM IN THE UPPER AIR PASSAGES OF HEALTHY PEOPLE \*

ARTHUR L BLOOMFIELD, MD

AND

AUGUSTUS R FELTY, MD

BALTIMORE

The study of an epidemic or of an outbreak of certain acute infectious diseases can perhaps best be approached from the standpoint of deviation from average or normal conditions. Such a mode of attack seems specially applicable to those infections caused by bacteria which may be harbored by carriers, and which are constantly present, at least to a certain extent, in the community, and the question which presents itself is why the apparent balance between parasite and host becomes upset, with a consequent spread of organisms and production of disease. The problem is tremendously complex and doubtless involves many unknown factors. However, in the recorded studies of epidemics, certain fairly definite alterations in the distribution of the causal bacteria among the general population have been observed, the carrier rate both among healthy contacts and healthy noncontacts almost invariably rises. During epidemics of meningitis, for example, the carrier rate may rise to 80 per cent among the contacts<sup>1</sup> in contrast to the average rate of about 2 per cent in nonepidemic times and under average conditions. A similar phenomenon has been noted with the diphtheria bacillus,<sup>2</sup> the fixed type pneumococci<sup>3</sup> and streptococci<sup>4</sup>.

It seems of great importance, then, in the intelligent study of the spread of respiratory infections, to know as definitely as possible the "average," "normal" or "mean" distribution of the causal bacteria in nonepidemic times, in order that a departure from such a distribution may be accurately correlated with the occurrence of cases of disease. Such studies may yield criteria which will be helpful in differentiating sporadic from epidemic disease, a distinction which, as will be shown later, cannot always be made on a basis of the number of cases alone.

In the present instance it was our plan to obtain control material which would later be of help in explaining the mode of spread of acute

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\*From the biologic division of the medical clinic, the Johns Hopkins University and Hospital.

1 Glover, J. *Hygiene* **17** 350, 1918.

2 Graham-Smith. *Bacteriology of Diphtheria*, Cambridge 1908, 1917.

3 Sydenstricker, V. P., and Sutton, A. C. *Bull. Johns Hopkins Hosp* **28** 312, 1917.

4 Blake, F. G. *Am. Otol., Rhinol., Laryngol.* **28** 361, 1919.

4 Studies to determine the degree of dissemination of hemolytic streptococcus from carriers to contacts in nonepidemic times

5 Relation of carrier state to history of previous streptococcus infection (tonsillitis)

#### MATERIAL AND METHODS

A group of about 200 women, students in the Johns Hopkins Hospital Nurses Training School, furnished material for the present study. Through the interested and intelligent cooperation of the supervisors of nurses, it was possible to keep the entire group under close observation, to obtain detailed information as to the exact location of their quarters in various dormitories, to obtain lists of room-mates, assignments to duty, etc., which were essential if useful contact studies were to be made. Furthermore, all cases of sickness, even mild colds, sore throats, or respiratory infections were reported daily to the resident physician of the hospital so that accurate data on the incidence of these conditions among the members of the group were available.

The bacteriologic survey for hemolytic streptococcus was made in the following way. A certain number of nurses reported to the laboratory daily for the taking of cultures. At that time a brief history and examination were recorded which included these points: the name, age, room number (dormitory), name of room-mate, date of entry to training school, history of colds or upper respiratory infections, history of tonsillitis, tonsillectomy (date), history of scarlet fever or other possible streptococcus infection, appearance of pharynx and tonsils with reference to size, crypts, scarring, adhesions, exudate, etc.

Three cultures were taken from each subject.

The first culture was taken from the pharynx. Taking care to avoid the tonsils and palate a straight cotton swab was vigorously rubbed over the posterior pharyngeal wall, covering the entire accessible area. The second culture was taken from the right tonsil. A 10 cm. piece of soft glass tubing 5 by 8 mm. in diameter was drawn out at one end to a capillary point about 1 to 1.5 mm. in diameter, and bent at an angle of 20 to 30 degrees. The wide end was stoppered with cotton, the pipet wrapped in paper and sterilized by dry heat. Before use a piece of rubber tubing about 15 cm. long was attached to the wide end over the cotton plug. With the tongue well depressed, the capillary tube was inserted deeply into one or more tonsil crypts, and material for culture was aspirated by suction on the rubber tube. With a little practice, this procedure became simple. One usually obtained from the depths of the tonsil a drop or two of thick white or gray granular or pasty material. It was also possible with the pipet to break adhesions over crypts and to approach the interior of tonsils which appeared superficially intact. We should like to emphasize again that this procedure is a simple and satisfactory one for studying the tonsillar flora. It caused the subjects less discomfort than swabbing the throat, and there were no accidents or untoward effects from the manipulation. A third culture was taken from the left tonsil. The same method was used as in taking the culture from the right tonsil.

In subjects whose tonsils had been removed, a swab was taken from the pharynx and a second combined swab from both tonsil fossae.

The swabs from the pharynx and the material aspirated from the tonsils were immediately placed in tubes of meat infusion broth, and a series of dilutions were made in this medium. Small amounts of the diluted broth containing the bacteria were added to 10 cc. portions of 5 per cent human blood meat infusion agar (*pH* 7.4) which were shaken and poured into 15 cm. Petri plates. The plates were incubated at 37 C. and studied after twenty-four hours. The most difficult and essential point in the technic is to obtain an

tion (Fox and Hamburger,<sup>10</sup> Levy and Alexander<sup>11</sup>), but that this is not the only factor is indicated by the studies of Walker,<sup>12</sup> who found the incidence of hemolytic streptococcus in a military organization to be essentially the same (from 16 to 20 per cent) in the recruits arriving, in those departing, and in the permanent personnel. It is of interest that streptococcus disease was absent in this unit during the time of the study.

It is clear, then, that many problems remain in regard to the significance and potential activity of the hemolytic streptococci found in the throats of healthy people. As such activity is undoubtedly profoundly altered at times when streptococcus disease is highly prevalent, it seemed, as suggested above, that the first step should be a careful study of the nature of streptococcus parasitism in a group of healthy people under average conditions. With this as base line, it would be much easier to interpret the more complex findings in epidemic conditions.

In another place,<sup>13</sup> emphasis was placed on the importance of serial, quantitative and topographical cultures in explaining the significance of bacteria found in the upper air passages. It was pointed out that the mere recovery of an organism in itself meant little, unless quantitative and topographical data were obtained as well. Thus, a single colony of *Staphylococcus aureus* isolated on one occasion by throat culture might be of no significance, whereas hundreds of colonies of the same germ recovered on repeated occasions from a localized region, such as the tonsil, would undoubtedly indicate a focal infection. Furthermore, an organism which grows diffusely over the mucous membranes of the mouth and throat may have a different significance from one which is confined to a local focus of diseased lymphadenoid tissue.

An attempt was therefore made in the present work to study the following points:

- 1 The incidence of beta hemolytic streptococcus in the throats of healthy people under average conditions at a time when streptococcus disease was not prevalent

- 2 The exact location and the character of growth of hemolytic streptococcus in the throat under normal conditions to determine whether such growth is confined to a local focus (tonsil) or whether free growth on the mucous membranes take place

- 3 The effect of introduction of convalescent carriers into a group on the distribution of hemolytic streptococcus

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10 Fox, H, and Hamburger, W W. The Streptococcus Epidemic at Camp Zachary Taylor, Ky, J A M A 70 1758 (June 8) 1918

11 Levy, R L, and Alexander, H L. The Predisposition of Streptococcus Carriers to the Complications of Measles, J A M A 70 1827 (June 15) 1918

12 Walker, J E. J Infect Dis 27 618, 1920

13 Bloomfield, A L. The Serial Quantitative Method of Culture in the Study of Respiratory Disease, J A M A 77 187 (June 16) 1921

in a relative way the real distribution of the bacteria in the throat. It is obviously impossible to make the procedure of culture absolutely uniform in every case, and the error is doubtless on the side of missing occasional streptococcus carriers, although we feel sure that this will apply only to the rare transient carrier with an extremely slight degree of infestation.

TABLE 1—*Results of Cultures for Hemolytic Streptococcus in 108 Healthy Women Whose Tonsils Had Previously Been Removed*

Case Number	Date of Culture	Number of Colonies of Beta Hemolytic Streptococcus Recovered from Pharynx	Number of Colonies of Beta Hemolytic Streptococcus Recovered from Tonsil Fossae	Remarks
6	9/ 7/22	0	0	
7	9/ 7/22	0	0	
16	9/ 8/22	0	0	
17	9/ 9/22	0	0	
18	9/10/22	0	0	
22	9/11/22	0	0	
24	9/14/22	0	0	
28	9/14/22	0	0	
36	9/14/22	0	0	
37	9/14/22	Few†	0	Tonsillectomy 3 years ago
39	9/15/22	0	0	
41	9/15/22	0	0	
43	9/15/22	Few	Few	Tonsillectomy 11 years ago
44	9/15/22	0	0	
48	9/15/22	0	0	
51	9/18/22	Few	Few	Tonsillectomy 5 years ago
52	9/18/22	0	0	
76	9/18/22	0	0	
60	9/19/22	0	0	
62	9/19/22	0	0	
75	9/22/22	0	0	
77	9/22/22	0	0	
78	9/22/22	0	0	
79	9/22/22	0	0	
80	9/22/22	0	0	
82	9/25/22	0	0	
85	9/25/22	0	0	
90	9/25/22	0	0	
92	9/25/22	0	3	Tonsillectomy 1 year ago
94	9/25/22	0	0	
95	9/25/22	0	0	
96	9/25/22	0	0	
100	9/26/22	0	0	
101	9/26/22	0	0	
102	9/26/22	0	0	
104	9/27/22	0	0	
106	9/27/22	0	0	
107	9/27/22	0	0	
108	9/30/22	0	0	
111	9/30/22	0	0	
114	9/30/22	0	0	
115	9/30/22	0	0	

\* Total cases, 42, negative 38 or 90.5 per cent, positive, 4 or 9.5 per cent

† Few indicates less than six colonies, and less than 1 per cent of total colonies on plate

In every culture in which many colonies of hemolytic streptococcus were present, all seemed to be identical. This impression was almost invariably supported, as will be pointed out in a later paper, when several colonies were fished and studied. It is quite possible, however, that two or more strains of hemolytic streptococcus may occasionally be present in the same throat, but such a state of affairs would bear no significant relation to our conclusions.



abundance of colonies which are both well distributed and discrete so as to allow accurate counting and easy fishing. By using several dilutions it was possible in every case to obtain satisfactory plates.

*Study of the Plates*—Attention was confined practically to the beta type of hemolytic streptococcus. It seems hardly necessary to refer to the original definition of Smith and Brown<sup>14</sup> and to the later descriptions of Brown,<sup>15</sup> but suffice it to say that consideration was given only to organisms which produced a total and usually relatively wide (1 to 2 mm) zone of hemolysis about the colony, without any production of greenish discoloration. In the vast majority of cases there was no serious difficulty in picking out the real beta type colonies. In the occasional instance in which one seemed to be dealing with a borderline type—a colony about which the hemolytic zone was not absolutely complete, or one which together with hemolysis showed slight greenish discoloration—the difficulty was invariably cleared up on subculture when all such doubtful organisms were found definitely to be alpha or alpha prime and not beta types.

In each set of plates in which beta hemolytic streptococci were present, a careful note was made of the total number and of their relation to the other colonies. Special attention was given to the apparent identity of the hemolytic colonies when many were present, and a number of them (usually six) were fished to blood-agar slants, and preserved for further study. Later, practically all the strains were replated to insure purity, and were studied microscopically.

It may be stated at this point that no beta hemolytic strain has become essentially altered in its characteristics by subculture and storage—in no instance has any of them either lost their hemolytic activity or become green producers even after several months of artificial growth.

A word should be said about the terminology used in the following tables to express the number of colonies of beta hemolytic streptococcus recovered. No plate was considered satisfactory unless there was a heavy seeding of bacteria. When a note is made of "a few," "20," or any other small number of colonies of beta hemolytic streptococcus, these represent only a minute fraction of the total bacterial growth on the plate. On the other hand, when the designation "1/10" of the plate, "50 per cent" of the plate, or "pure culture" of beta hemolytic streptococcus is noted, it means not only a certain percentage of the total growth, but an absolutely large number of hemolytic streptococcus colonies as well. Furthermore, the results as expressed represent only

14 Smith, T., and Brown, J. H. J. M. Res. **31** 455, 1915

15 Brown, J. H. Monograph 9, Rockefeller Institute, 1919

TABLE 2—Results of Cultures for Hemolytic Streptococcus in 108 Healthy Women Whose Tonsils Had Not Been Removed<sup>\*</sup>

Case No	Date	Number of Colonies of Beta Hemolyticus Streptococcus from			Appearance of Tonsils	History of Tonsillitis
		Pharynx	Right Tonsil	Left Tonsil		
2	9/ 7/22	0	0	0	Medium, clean, many crypts	Negative
3	9/ 7/22	0	0	0	Large, clean, many crypts	Negative
4	9/ 7/22	0	0	0	Small stumps, partial tonsillectomy	Last attack 8 yrs ago
5	9/ 7/22	0	0	0	Small clean, no visible crypts	Last attack 8 mos ago
8	9/ 7/22	0	0	0	Huge, scarred adhesions, many large crypts	Last attack 1 yr ago
9	9/ 7/22	0	0	0	Small, clean, many crypts	Negative
10	9/ 7/22	0	No culture	0	Small, clean, deep set, no crypts seen	Negative
11	9/ 7/22	0	Many 50% of plate	0	Large, globular, clean, concealed crypts	Last attack within last 9 mos
12	9/ 8/22	0	Many 10% of plate	0	Large, scarred adhesions, many sealed crypts	Last attack 6 mos ago
13	9/ 8/22	0	0	0	Small, clean, deep set, few sealed crypts	Last attack 10 yrs ago
14	9/ 8/22	0	0	0	Very large globular tonsils	No attack for several years
19	9/11/22	0	0	0	Very small, clean, many crypts	One attack 2 yrs ago
20	9/11/22	0	0	0	Very small, clean, few sealed crypts	Negative
21	9/11/22	0	No culture	0	Small stumps with crypts, partial tonsillectomy	Last attack 2 yrs ago
25	9/12/22	0	0	0	Small, clean, deep set	Negative
26	9/12/22	0	0	0	Large, clean, scarred	Last attack 1½ yrs ago
27	9/15/22	0	Many 10% of plate	Many 10% of plate	Large, clean, scarred	Last attack 1½ yrs ago
28	9/15/22	0	0	0	Huge, globular, many crypts	Last attack 6 yrs ago
29	9/15/22	1% of plate	50% of plate	33% of plate	Very small, deep set, clean	No attack for yrs
30	9/15/22	20 colonies	2 colonies	0	Large, scarred, many crypts	Last attack 10 mos ago
33	10/ 7/22	0	0	0	Medium, many crypts	Last attack 2 mos ago
38	9/15/22	0	0	0	Small, deep set, many crypts	Last attack 9 yrs ago
40	9/15/22	20% of plate	Many pure cult	0	Huge, congested, many sealed crypts	Last attack 11 mos ago
42	9/15/22	1% of plate	1% of plate	1% of plate	Large, ragged, scarred	Last attack 1 yr ago
45	9/15/22	many	many	many		
45	9/15/22	20% of plate	80% of plate	0	Very small, clean	Last attack 4 yrs ago
46	9/16/22	0	0	0	Very large, clean, scarred	Last attack 4 mos ago
47	9/18/22	0	0	0	Medium, deep set, clean, scarred	Negative
49	9/18/22	4 colonies	Almost pure cult	0	Large, globular, clean	Negative, scarlet fever 1 yr ago
50	9/18/22	0	1% of plate	1% of plate	Very large, clean, many crypts	Last attack 8 mos ago
53	9/18/22	0	0	0	Very large, globular scarred, clean	Last attack 4 yrs ago
54	9/18/22	0	No culture	0	Small, deep set, clean	Negative
55	9/18/22	1 colony	Almost pure cult	Many over 10%	Deep set, clean	Last attack 6 mos ago
57	9/18/22	0	No culture	Many over 10%	Huge, scarred, ragged especially left	No attack for 13 years
58	9/20/22	Few	20 colonies	3 colonies	Huge, clean, many crypts	Last attack 5 mos ago
59	9/20/22	0	No culture	0	Very small, deep set	Last attack 5 yrs ago

\* Total cases, 66, negative 39, or 59 per cent, positive 27, or 41 per cent

## RESULTS

*Incidence and Distribution of Beta Hemolytic Streptococcus in the Throats of Healthy People at a Time When Streptococcus Disease Was not Prevalent*—During the month of September, 1922, cultures were made from 108 healthy students. There had been one case of acute tonsillitis in the training school during the last week of August, but no cases during June or July, and there were no cases during September. The experiment, therefore, seemed absolutely valid from the standpoint of representing "average" or "normal" conditions in a community at a time when streptococcus infection (tonsillitis) was not present.

The results of the cultures are given in Tables 1 and 2. Thirty-one, or 28.7 per cent, of the total group of 108 yielded beta hemolytic streptococcus. A study of the tables, however, immediately discloses a remarkable difference between those whose tonsils have been removed and those in whom the tonsils are intact. Of the former group of forty-two people, only four, or 9.5 per cent, harbored the organism and only in small numbers. Occurrence of a few scattered colonies of a foreign organism on the mucous membrane of the throat indicates almost always, as we have shown elsewhere,<sup>16</sup> an insignificant transient infestation. It seems perfectly clear that these tonsillectomized persons were not the subjects of a chronic carrier state and that the organisms had been introduced by chance, perhaps from another person and were of no more significance than an inanimate foreign particle. On the other hand, the group of persons whose tonsils were intact exhibited entirely different conditions. A much larger percentage of the group (41 per cent) were carriers, and the number and distribution of the bacteria were different. A study of Table 2 shows that in this group the hemolytic streptococcus carrier state was essentially one of focal tonsillar infection. The streptococci were recovered with frequency and often in huge numbers from the depths of the tonsils when not a single colony was obtained from the pharynx, and in no case were they obtained from the pharynx unless the tonsil culture showed them as well, and usually in much greater numbers. It is certain, as we have shown elsewhere,<sup>17</sup> that in most of these people the streptococci recovered from the pharynx represented merely an overflow or spread by direct contact from the breeding place in the tonsil, and that they were not actually colonizing and growing on the free mucous membrane.

**Summary**—These cultures allow an exact definition of the nature of beta hemolytic streptococcus parasitism under average conditions in healthy people when streptococcus disease is not present. Such parasitism is strictly a focal one in areas of infected lymphadenoid tissue,

16 Bloomfield, A. L. *Bull. Johns Hopkins Hosp.* **32**: 290 (Sept.) 1921.  
17 Bloomfield, A. L. *A. J. M. Sc.* **164**: 854, 1922.

began to appear in the group, and during this month there were nine cases. All these patients yielded innumerable colonies of hemolytic streptococci from the throat and tonsils. After an average hospitalization of one week, they reentered the group, although culture showed that they still harbored tremendous numbers of hemolytic streptococcus. To determine whether the occurrence of tonsillitis was associated with any change in the normal type of parasitism defined above, as well as to study the effect of introducing heavily infected convalescent carriers into the group, a set of cultures was made during October, 1922, on a second series of sixty-seven healthy subjects similar in every way to the first, both as to methods and material. The results are analyzed in Tables 3 and 4, and are summarized in Table 5.

TABLE 3—*Results of Cultures for Hemolytic Streptococcus in Healthy Women Whose Tonsils Had Previously Been Removed\**

Case Number	Date of Culture	Number of Colonies of Beta Hemolytic Streptococcus Recovered from		Remarks
		Pharynx	Tonsils	
121	10/ 9/22	0	0	Tonsillectomy 3 weeks ago
122	10/ 9/22	0	0	
123	10/ 9/22	0	0	
124	10/ 9/22	0	0	
133	10/10/22	0	0	
134	10/10/22	0	0	
136	10/10/22	0	0	
139	10/10/22	1	0	
140	10/10/22	0	0	
142	10/10/22	0	0	
145	10/11/22	0	0	
147	10/11/22	0	0	
152	10/13/22	0	0	
157	10/16/22	0	0	
158	10/16/22	0	0	
159	10/16/22	0	0	Tonsillectomy 2 months ago
160	10/16/22	0	0	
168	10/16/22	0	0	
169	10/18/22	0	0	
171	10/18/22	Practically pure culture	1	
174	10/18/22	0	0	
178	10/18/22	0	0	
182	10/20/22	0	0	
187	10/20/22	0	0	
191	10/20/22	0	0	

\* Total cases, 25, positive 2, or 8 per cent, negative 23, or 92 per cent.

A study of these tables shows a striking agreement between the two sets of cultures both as to the total incidence of beta hemolytic streptococcus and as to the quantitative topographical distribution of the bacteria. As a matter of fact, the percentage of positives was a little lower after streptococcus disease became prevalent. Case 171 was the single exception, showing a practically pure culture from the pharynx of a tonsillectomized person, but it should be noted that the tonsils were removed only two months previous to culture, and that a stump was left on one side.

TABLE 2—(Continued)

Case No	Date	Number of Colonies of Beta Hemolyticus Streptococcus from			Appearance of Tonsils	History of Tonsillitis
		Pharynx	Right Tonsil	Left Tonsil		
61	9/20/22	0	50% of plate	50% of plate	Large, deep set, clean	Last attack 6 yrs ago
63	9/20/22	0	0 surface culture	0 surface culture	Tonsils not definitely visible	Last attack 5 yrs ago
64	9/20/22	0	No culture	1 colony	Very small, deep set, few large crypts	Two attacks in past year
65	9/20/22	Many colonics	Many colonies, surface cult	Many colonies, surface cult	No tonsil visible	Last attack 6 mos ago
66	9/20/22	0	No culture	0	Medium, clean	Negative
67	9/20/22	0	0	0	Very small, deep set	Negative
68	9/20/22	0	0	0	Very small, clean, deep set	Negative
70	9/22/22	0	0 surface culture	0 surface culture	Partial tonsillectomy, large stumps	Last attack 6 yrs ago
71	9/22/22	0	0	0	Small, clean	Negative
72	9/22/22	0	0 surface culture	0 surface culture	Small, clean	None recently
73	9/22/22	Few	No culture	No culture	Small, deep set	None recently
76	9/22/22	Few	50% of plate	50% of plate	Partial tonsillectomy, small stumps	Last attack 9 mos ago
81	9/25/22	No culture	Few	Few	Large, deep set, clean	None recently
83	9/25/22	0	0	0	Large, scarred, clean, many crypts	Last attack 7 mos ago
84	9/25/22	0	0	50% of plate	Large, clean	Negative
86	9/25/22	0	0	Few, less than 1%	Small, deep set, ragged, clean	Last attack 7 yrs ago
87	9/22/22	0	0	0	Small, clean, deep set	Last attack 15 yr ago
88	9/25/22	0	surface almost pure cult	0	Large, clean	Negative
89	9/25/22	0	0	0		Negative
91	9/25/22	Few	Few	Few	Small, clean tonsils	Last attack 1913
93	9/25/22	0	0	0	Huge, globular, clean, many crypts	None recently
97	9/26/22	0	0	0	Clean, large many crypts	Last attack 1 yr ago
98	9/26/22	0	0	0	Large, clean, deep set	Last attack 5 yrs ago
100	9/26/22	0	0	0	Large, clean	Last attack 1 yr ago
103	9/27/22	0	Many	Almost pure cult	Large, ragged, deep set	Last attack 1 yr ago
105	9/27/22	0	0	0	Small, deep set, clean	None recently
109	9/30/22	0	0	0	Small, clean	Negative
110	9/30/22	0	0	0	Small, ragged	Negative
112	9/30/22	Few	0	Very few	Small, deep set	Last attack 5 yrs ago
113	9/30/22	0	Few	0	Large, clean	Last attack 1 yr ago
116	9/30/22	0	0	0	Medium, deep set	Last attack 3 yrs ago

such as the tonsil, and there is no evidence that the bacteria are actually growing and multiplying on the free surfaces of the mucous membrane, although a few may be spread by direct contact from the tonsil over the pharyngeal wall. The occasional colony recovered from tonsillectomized persons clearly indicates, as a rule, a transient "pick-up" and not a true chronic carrier state.

*Effect of Occurrence of cases of Tonsillitis and Introduction of Convalescent Carriers into the Group on the Type of Streptococcus Parasitism*—During the early part of October, 1922, acute tonsillitis

**Summary** The occurrence of acute tonsillitis was unassociated with any general change in streptococcus parasitism in the group, nor did the reintroduction of heavily infected convalescent carriers produce any alteration. This point will be developed in a later paper in connection with the epidemiology of tonsillitis.

*Dissemination of Hemolytic Streptococcus from Carriers to Contacts During a Nonepidemic Time*—The preceding observations seemed to indicate that under ordinary conditions, when streptococcus disease was not epidemic, there was no tendency to the development of secondary carriers by contact between the uninfected and infected healthy members of the group. To settle this point, an analysis was made of fifty-one pairs of room-mates. These pairs had been rooming together for at least several weeks before the cultures were made, and there had been every opportunity for close contact. The results of the cultures are shown in Table 6. On the law of chance alone, one would have expected at least eight pairs to be positive instead of four, so that there can be no question but that contact between healthy people played no part in the establishment of the carrier state in this group.

TABLE 5—*Comparison of Cultures Made Before and After Streptococcus Disease (Tonsillitis) Was Prevalent*

Series	Tonsillectomized			Nontonsillectomized		
	Total	Percentage Positive	Percentage Negative	Total	Percentage Positive	Percentage Negative
I September, 1922, before streptococcus disease appeared	42	9.5	90.5	66	41.0	59.0
II October, 1922, after streptococcus disease appeared	25	8.0	92.0	42	33.0	67.0
Combined total	67	9.0	91.0	108	37.0	63.0

*Relation of Carrier State to Previous Streptococcus Infection (Tonsillitis)*—It was clear, then, that some other explanation besides contact must be sought to explain the occurrence of streptococcus carriers. As the organisms were essentially confined to the tonsil, it seemed possible that all the carriers dated from an original acute streptococcus infection of the tonsil (tonsillitis). From 130 members of our group, it was possible to obtain accurate statements as to preceding acute attacks. These histories correlated with the bacteriologic findings are analyzed in Table 7. The figures suggest strongly that the foregoing assumption is correct and that the chronic carrier state represents a residue of an acute tonsillitis. The 20 per cent of carriers in the group with negative history may be partly explained by infection dating from a mild attack of tonsillitis which did not impress the patient. We have had the opportunity to observe several such cases which were

TABLE 4—Results of Cultures for Hemolytic Streptococcus in Healthy Women Whose Tonsils Had Not Been Removed \*

Case No	Date	Number of Colonies of Beta Hemolytic Streptococcus from			Appearance of Tonsils	History of Tonsillitis
		Pharynx	Right Tonsil	Left Tonsil		
125	10/ 9/22	0	0 surface culture	0 surface culture	Partial tonsillectomy 4 years before, stumps ragged	No attack for 4 years
126	10/ 9/22	0	0	0	Huge, ragged	Last attack 1 year ago
127	10/ 9/22	0	0	0	Large, clean	Negative
128	10/ 9/22	0	0	0	Small, clean, deep set	Negative
131	10/10/22	0	0	0	Medium, ragged	Last attack 1 year ago
132	10/10/22	Few	Almost pure cult	Almost pure cult	Huge, clean, large crypts	Last attack 3 yrs ago
135	10/10/22	Few	Few	0	Large, ragged, scarred	Negative
137	10/10/22	0	Few	Few	Very large, ragged	Last attack 1 year ago
138	10/10/22	0	0	0	Small, clean	Negative
141	10/10/22	0	0	0	No definite tonsils visible	None recently
143	10/11/22	0	0 surface	0 surface	Large, clean	Negative
144	10/11/22	0	0	0	Right tonsil not seen, left tonsil small, clean	Negative
146	10/11/22	0	0	0	Huge, clean, many crypts	Negative
148	10/11/22	0	0	0	Large, clean	Negative
149	10/11/22	0	Many 10% of plate	Many 10% of plate	Small, deep, clean	Negative
150	10/11/22	0	0	0	Small, clean	Last attack 9 mos ago
151	10/13/22	0	0 surface	0 surface	Small, clean	Last attack 15 months ago
153	10/13/22	0	0	Few	Moderate, adherent, clean	Last attack 7 mos ago
154	10/13/22	1	Very many over 10%	Many over 10%	Small, clean	None recently
155	10/13/22	0	0	0	Medium, adherent, clean	Last attack 4 yrs ago
156	10/13/22	0	0	0	Medium, adherent, clean	Last attack 17 yrs ago
161	10/16/22	0	0	0	Medium, clean	Last attack 3 mos ago
162	10/16/22	0	0	0	Small, clean	Last attack 4 yrs ago
163	10/16/22	0	0	0	Medium, clean	Negative
164	10/16/22	0	No cultures	0	Medium, clean	Negative
165	10/16/22	1 colony	Few	0	Large, clean	Negative
167	10/16/22	0	0	0	Large, ragged	Negative
170	10/18/22	0	0	0	Large, clean	Last attack 2 yrs ago
172	10/18/22	0	0	0	Medium, clean	Negative
173	10/18/22	Few	0	Few	Medium, clean	Last attack 2 yrs ago
175	10/18/22	0	0	0	Medium, clean	Last attack 20 months ago
176	10/18/22	0	0	50% of plate	Small, clean	Last attack 8 mos ago
179	10/18/22	0	0 surface	0 surface	Medium, ragged	Negative
183	10/20/22	Few	Few	Few	Small, clean, crypts	Negative
184	10/20/22	0	0	0	Large, ragged	Negative
185	10/20/22	0	0	0	Very small, barely visible	Negative
186	10/20/22	0	1 colony, surface swab both tonsils	0	Partial tonsillectomy, ragged stumps, crypts	Negative
188	10/20/22	0	0	0	Very large, clean	Negative
189	10/20/22	1 colony	Almost pure cult	0	Very large, clean	Negative
190	10/20/22	0	Pure culture	Pure culture	Large, ragged, clean	Negative
192	10/20/22	0	Many	Many	Large, clean	Negative
193	10/20/22	0	0	0	Very large, ragged, clean	Last attack 8 yrs ago

\* Total cases, 42, positive 14, or 33 per cent, negative 28, or 67 per cent

—the type usually condemned by the laryngologist, and Group 2, tonsils intermediate in appearance between Groups 1 and 3. The results of culture in the three groups are summarized in Table 8.

TABLE 7—*Relation of Streptococcus Carriage to History of Tonsillitis*

History of an Attack of Tonsillitis	Total Number of Cases	Percentage Positive for Beta Hemolytic Streptococcus
Within 6 months before culture	30	83.4
Six months to two years before culture	27	52.0
Over two years before culture	33	33.3
No history of tonsillitis	40	20.0

TABLE 8—*Relation of Appearance of Tonsil to Positive Culture of Streptococcus Hemolyticus*

Group	Total Number of Cases	Number Positive	Percentage Positive
1	38	12	30.2
2	27	9	33.3
3	33	16	49.0

It appears that the obviously diseased tonsils yield hemolytic streptococcus more often than those of innocent appearance, although the latter are frequently infected with this organism.

#### SUMMARY AND DISCUSSION

Despite the great amount of clinical, biometric and bacteriologic study which is on record, no general laws have been deduced which are altogether satisfactory in explaining the spread of bacterial infection. It appears that the operation of different forms of infectious agents under various conditions may be so diverse that epidemic phenomena, while resembling each other in a broad way, may be quite dissimilar in their intimate details. In the case of the present problem—infection with *Streptococcus hemolyticus*—the useful mode of approach has seemed to be from the standpoint of the deviation from the “normal,” “average,” or “mean” type of parasitism of this organism, and the immediate object of this report is to define in as accurate terms as possible such a “norm.” A detailed study has therefore been made of the quantitative topographical distribution of hemolytic streptococcus in the upper air passages of an average group of healthy persons and of the effect of certain possible disturbing factors on such a distribution.

The major conclusion is that the hemolytic streptococcus under average conditions is strictly adapted to a local growth in foci of lymphadenoid tissue in the upper air passages, especially the tonsil. In such foci these bacteria may persist for long periods of time and



quite definite but which were unassociated with fever or much sore throat. They will be discussed later in connection with the clinical features of tonsillitis.

TABLE 6—Occurrence of Hemolytic Streptococcus in Room-Mates

Case Number	Date of Culture	Hemolytic Streptococcus	Case Number	Date of Culture	Hemolytic Streptococcus	Case Number	Date of Culture	Hemolytic Streptococcus
193	10/20/22	Negative	153	10/13/22	Positive	115	9/30/22	Negative
190	10/20/22	Positive	106	9/27/22	Negative	6	9/ 7/22	Negative
191	10/20/22	Negative	151	10/13/22	Negative	112	9/29/22	Positive
165	10/16/22	Positive	58	9/20/22	Positive	88	9/22/22	Positive
189	10/20/22	Positive	148	10/11/22	Negative	111	9/20/22	Negative
160	10/16/22	Negative	46	9/16/22	Negative	48	9/18/22	Negative
188	10/20/22	Negative	147	10/11/22	Negative	109	9/29/22	Negative
173	10/20/22	Positive	126	10/ 9/22	Negative	66	9/20/22	Negative
187	10/20/22	Negative	146	10/11/22	Negative	108	9/29/22	Negative
97	9/26/22	Negative	19	9/18/22	Positive	64	9/20/22	Negative
186	10/20/22	Positive	145	10/11/22	Negative	98	9/26/22	Negative
175	10/18/22	Negative	103	9/26/22	Positive	67	9/20/22	Negative
184	10/20/22	Negative	144	10/11/22	Positive	93	9/22/22	Negative
65	9/20/22	Positive	89	9/25/22	Negative	94	9/22/22	Negative
183	10/20/22	Positive	141	10/10/22	Negative	84	9/24/22	Positive
170	10/18/22	Negative	128	10/ 9/22	Negative	4	9/ 7/22	Negative
171	10/18/22	Positive	139	10/10/22	Positive	74	9/21/22	Negative
179	10/18/22	Negative	116	9/29/22	Negative	28	9/12/22	Negative
163	10/16/22	Negative	136	10/10/22	Negative	73	9/21/22	Positive
176	10/18/22	Positive	102	9/26/22	Negative	2	9/24/22	Negative
192	10/20/22	Positive	135	10/10/22	Positive	71	9/21/22	Negative
174	10/18/22	Negative	38	9/15/22	Negative	40	9/15/22	Positive
80	9/22/22	Negative	133	10/10/22	Negative	68	9/19/22	Negative
172	10/18/22	Negative	42	9/15/22	Positive	50	9/18/22	Positive
168	10/18/22	Negative	132	10/10/22	Positive	63	9/20/22	Negative
164	10/16/22	Negative	37	9/15/22	Positive	60	9/20/22	Negative
72	9/22/22	Negative	131	10/10/22	Negative	61	9/20/22	Positive
162	10/16/22	Negative	55	9/18/22	Positive	57	9/18/22	Positive
161	10/16/22	Negative	127	10/ 9/22	Negative	54	9/18/22	Negative
156	10/13/22	Negative	121	10/ 9/22	Negative	53	9/18/22	Negative
138	10/10/22	Negative	125	10/ 9/22	Negative	50	9/18/22	Positive
155	10/13/22	Negative	17	9/16/22	Negative	36	9/15/22	Negative
110	9/29/22	Positive	123	10/ 9/22	Negative	33	10/ 7/22	Negative
154	10/13/22	Positive	41	9/15/22	Negative	15	9/ 9/22	Positive
14	9/ 8/22	Negative						

Total pairs of room mates, 51, both positive, 4, both negative, 23, one positive, one negative, 24

*Relation of Streptococcus Carriage to Appearance of Tonsil*—Finally, it seemed of interest to correlate the presence of the hemolytic streptococcus with the clinical appearance of the tonsils. A sharp classification was impossible. However, we have divided the tonsils into three groups. Group 1, small, clean, without adhesions, scars or large crypts—tonsils of “innocent” and insignificant appearance, Group 3, large, scarred, or adherent tonsils usually with plugged crypts

# STUDIES ON LIVER FUNCTION

## ROSE BENGAL ELIMINATION FROM THE BLOOD AS INFLUENCED BY LIVER INJURY<sup>1</sup>

G D DELPRAT, JR., M D  
SAN FRANCISCO

In recent years, the interest of a number of investigators has centered on the question of liver function. It is hardly necessary at the present time to discuss these tests in detail as a review by Delprat and Whipple<sup>1</sup> covers much of this ground. Whipple and Pelkan<sup>2</sup> have recently reported experiments which indicate that phenol conjugation is a function of the liver which gives information of value in a study of the physiology of the liver. Phenol ingestion is too toxic for clinical use. Many papers<sup>3</sup> dealing with the injection of phenoltetrachlorophthalein have appeared during the past few years. This dye is eliminated promptly from the blood by the liver and appears in the bile and intestine. Various methods of recovery of the dye from the feces or duodenum have been used, but this test is inaccurate when there are abnormalities of the biliary passages and therefore has obvious clinical limitations. Since the completion of these experiments, two papers by Rosenthal<sup>4</sup> have appeared dealing with a utilization of tetrachlorophthalein in the blood stream. His experiments were almost identical with the experiments given below in which a new dye, rose bengal is used. Our experiments in many respects confirm the observations of Rosenthal.

An ideal dye for this type of work must fulfil the following requirements: (a) It must be nontoxic, (b) it must be a crystalloid (we know that the fate of colloid dyes in the organism is entirely different from that of the diffusible dyes), (c) it must be eliminated from the organism by means of the activity of liver parenchyma cells, and (d) it must remain in the circulation for a sufficient length of time to allow determinations of the dye concentration in the blood plasma to be made. All these requirements are fulfilled in the substance rose bengal.

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From the George Williams Hooper Foundation for Medical Research, University of California Medical School, San Francisco.

1 Delprat, G D, and Whipple, G H. *J Biol Chem* **49** 229, 1921.

2 Whipple, G H, and Pelkan, F K. *Biol Chem* **50** 513, 1922.

3 Rowntree, L G, Hurwitz, S H, and Bloomfield, A L. *Bull Johns Hopkins Hosp* **24** 327, 1913. McNeil, H L. *J Lab & Clin Med* **1** 822, 1916. Whipple, G H, Peightal, T C, and Clark, A H. *Bull Johns Hopkins Hosp* **24** 343, 1913.

4 Rosenthal, S M. *J Pharm & Exper Therap* **19** 385, 1922, *Proc Soc Exper Biol & Med* **20** 86, 1922.

in great numbers—we obtained no evidence of a free growth on the mucous membranes in general. It appears, furthermore, that such colonization is usually brought about by an acute, clinically manifest, infection of the lymphadenoid tissue, such as acute tonsillitis, or perhaps scarlet fever. Such an infection seems necessary, under average conditions, in order that the bacteria may gain a lasting foothold. Careful study of carriers and noncarriers who roomed together seemed to prove that mere contact, even if close and prolonged, is inadequate—under average conditions—to give rise to new carriers. Again, it was found that neither the incidence of healthy carriers nor the local lymphoid tissue type of parasitism was altered by introducing into the group tonsillitis convalescents harboring presumably actively vegetative organisms. The exact relationship of preexisting carriers to fresh cases of acute tonsillitis will be discussed in a subsequent paper.

Finally, further evidence of the essentially focal nature of hemolytic streptococcus parasitism under “normal” conditions is found in the fact that of those whose tonsils have been removed only an occasional person harbored the organism, and then in small numbers, indicating a transient infestation rather than a true growth adaptation.

Such then is the definition of the status of streptococcus hemolyticus parasitism under normal conditions when streptococcus disease is either absent or sporadic in type. But observations on record in the literature show that when streptococcus disease is highly epidemic, a type of parasitism which is quite different may exist. Under such conditions, for example in the army camps, it was found<sup>4</sup> that practically every man both sick and well was a streptococcus carrier, and also that the organisms apparently were growing freely and generally on the mucous membrane of the throat, and were by no means confined to local lymphadenoid foci. A radical change in the type of parasitism had occurred. The nature and significance of this change will be discussed at another time. At present the fact is mentioned to stress by contrast the “normal” or “average” stable type of parasitism described above, which apparently must be fundamentally upset before epidemic streptococcus disease can occur.

centrifuge tube containing 2 c c of 2 per cent potassium oxalate solution This is a control sample

(3) With the needle in situ, the solution of the dye in the syringe which was laid aside is injected into the circulation and the time is noted The plunger is drawn back and forth to rinse out the barrel and the needle, this process being continued until the next step The last manipulation reduces the amount of dye that may possibly remain in the needle to an extremely small quantity, which may then be neglected

(4) One minute from the time of the beginning of the injection a sample of from 8 to 10 c c of blood is withdrawn into a clean syringe, and is delivered into a centrifuge tube identical with the one previously used

(5) At two, four, eight and sixteen minutes from the time when the injection began, samples of blood are withdrawn from the jugular vein, and are delivered into centrifuge tubes containing a solution of potassium oxalate It is usually advisable to withdraw the needle after taking the four minute sample and to make a fresh puncture for both the eight and the sixteen minute samples, to avoid the possibility of clot formation

(6) The six centrifuge tubes containing the samples are then centrifugalized for thirty minutes at 3,000 revolutions per minute

(7) After noting the volume of blood in the graduated centrifuge tubes, 3 c c of plasma from each of the samples are delivered into a clean test tube, and are diluted with 6 c c of normal saline, care being taken to wash the pipet with saline before it is used for the next specimen Samples of each of these diluted plasma solutions are then placed in a Hellige colorimeter and read against a standard prepared as follows Five c c of normal blood plasma (from the control tube) are diluted with 5 c c of saline, and to this are added 5 c c of a 0.0075 per cent solution of the rose bengal (made by diluting 0.75 c c of a 1 per cent solution of the dye to 100 c c distilled water)

(8) Allowance must be made for the volume of the oxalate solution which is added to the blood in the hematocrit tube If 10 c c of blood are added to 2 c c of oxalate, it is evident that the colorimetric reading must be multiplied by 12/10 to allow for the dilution of the blood These corrected readings are given in the tables

EXPERIMENTS SHOWING RATE OF ELIMINATION OF DYE FROM BLOOD  
STREAM AND THE INFLUENCE OF LIVER INJURY ON  
RATE OF ELIMINATION

Experiments were carried out on dogs whose livers were injured by chloroform to determine the rate of disappearance of rose bengal after injection into the blood stream In each instance the rate of dis-

(tetraiodotetrabrom fluorescene) This substance is nontoxic in large doses (3 gm were tolerated by a 30 pound (13.6 kg) dog while 5 gm were fatal in five hours), it is a crystalloid, and it remains in the normal circulation

In 1918, an opportunity was afforded me for a study of a large series of the fluorescene and triphenylmethane dyes for the purpose of finding a "liver function dye" This work was carried out in the anatomical laboratory of the University of California under the guidance of Dr H M Evans The first experiments were carried out on rats, and those dyes which (after injection into the circulation of the animal) appeared only in the stools were subsequently injected into dogs with bile fistula Several of the dyes which in the rat were eliminated only in the stools were excreted in the urine of the dog However, one dye, rose bengal, was found to be eliminated entirely in the bile of both the rat and dog, even when injected in large doses At no time did it appear in the urine

Attempts were made to carry out determinations to ascertain the percentage of recovery in the bile On account of the interference of the bile pigments, colorimetric estimations of small amounts of the rose bengal were impossible with any degree of accuracy, and chemical methods by which the bile pigments were precipitated were unsatisfactory, since part of the dye was carried down in the precipitate

If the liver is the only organ concerned with the elimination of the dye, as it appears to be, then the rate of disappearance of the dye from the blood stream after injection should be definitely influenced by the liver activity or by the extent of the liver injury It is to be expected that the dye will remain longer in the circulation of the animal whose liver is injured than in the blood stream of the normal animal

#### METHOD

The method which was used in the following experiments is almost similar to the "dye method" of determining plasma volume<sup>5</sup> It may be briefly outlined as follows

(1) A measured amount of a 1 per cent solution of the dye is delivered into an evaporating dish and drawn into a 10 cc record syringe The evaporating dish is rinsed with a few drops of saline, which is also drawn into the syringe, and the rinsing is repeated until the evaporating dish shows no traces of the dye This syringe is then laid aside

(2) About 10 cc of blood are drawn from the jugular vein of the dog into a clean syringe, and in turn are delivered into a graduated

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<sup>5</sup> Hooper, C W, Smith, H P, Belt, A E, and Whipple, G H *Am J Physiol* **51** 205, 1920

TABLE 2—*Percentage Concentration of Rose Bengal in the Blood Plasma before and After Liver Injury by Chloroform Anesthesia*

Dog 22-40 (Adult Black and White Hound)\*

Date, 1922	Colorimetric Readings and Values for R at Intervals of									Weight, Pounds	Plasma Volume, Cc
	One Minute,	2 Minutes		4 Minutes		8 Minutes		16 Minutes			
	Per- cent- age	Per- cent- age	R	Per- cent- age	R	Per- cent- age	R	Per cent age	R		
3/28	61	56	0.92	46	0.76	31	0.51	26		22.8	662
3/29	61	57	0.95	49	0.81	31	0.52	31		22.5	662
3/31	64	61	0.95	41	0.64			30		21.5	622
4/ 3	Chloroform anesthesia 60 minutes										
4/ 3	78	72	0.93	63	0.81	53	0.67	46		19.8	512
4/ 4	91	86	0.95	(77)	(0.85)	(71)	(0.78)	(78)	0.86	19.3	438
4/ 5	89	83	0.94	80	0.90	77	0.86	63	0.70	18.8	450
4/ 6		81		69		57		50		18.0	

\* The dog was isolated on March 25 so that at the time of the anesthesia he had been fasted nine days. The experiment on April 3 was carried out six hours after the chloroform anesthesia. On April 3 and 4, the dog was quiet, drank a good deal of water but did not vomit. Clinically he was moderately toxic. The blood plasma was tinged yellow on April 3 and 4. The bracketed figures indicate that hemolysis accidentally occurred and that consequently the readings are somewhat inaccurate. The dose of rose bengal equals 30 mg. for each injection.

TABLE 3—*Percentage Concentration of Rose Bengal in the Blood Plasma before and After Liver Injury by Chloroform Anesthesia*

Dog 22-41 (Gray Adult Police Dog)\*

Date, 1922	Colorimetric Readings and Values for R at Intervals of										Weight, Pounds	Plasma Volume, Cc
	One Minute, Per- cent- age	2 Minutes		4 Minutes		8 Minutes		16 Minutes				
		Per- cent- age	R	Per- cent- age	R	Per cent age	R	Per cent age	R			
3/17	72	60	0.83	35	0.49	24	0.33	20	0.28	40 0	1,108	
3/18	73	63	0.86	45	0.62	27	0.37	20	0.27	20 0	1,098	
3/19	Chloroform anesthesia 45 minutes											
3/20	83	74	0.89	67	0.81	58	0.70	47	0.57	37 5	965	
3/21	89	87	0.98	83	0.93	71	0.79	59	0.66		902	
3/22	89	85	0.96	77	0.87	66	0.74	58	0.65		902	
3/24	90	79	0.88	68	0.76	49	0.54	40	0.44	37 5	890	
3/27		80		62		48						

\* On March 20 and 21 the dog was quiet, drank a good deal of water but he did not vomit. On March 20 the blood plasma was very dark yellow and progressively less so on the subsequent days. The dog fasted for a period of five days prior to the period of anesthesia. The dose of rose bengal equals 30 mg. for each injection.

TABLE 4—*Percentage Concentration of Rose Bengal in the Blood Plasma before and After Liver Injury by Chloroform Anesthesia*

Dog 22-37 (Adult Male Bull Terrier)\*

Date 1922	Dose of Rose Ben gal, Mg	1 Min- ute, %	Colorimetric Readings and Values for R at Intervals of												Weight, Pounds	Plasma Volume, Cc
			2 Minutes		4 Minutes		8 Minutes		16 Minutes		32 Minutes		46 Minutes			
			%	R	%	R	%	R	%	R	%	R	%	R		
2/15	30	104	98	0.93	76	0.73	54	0.52	32	0.31					24.8	384
2/16	30	93	72	0.78	65	0.70	47	0.49	29	0.31					24.0	431
2/16	Chloroform anesthesia 55 minutes															
2/17	20	71	85	1.12	63	0.88	66	0.92	59	0.83					23.8	374
2/18	20		77		66		61		57		47		37		23.5	
2/24	20	71	64	0.91	53	0.75	41	0.58	31	0.44	18	0.26	12	0.17		379
2/28	20	70	63	0.90	52	0.75	38	0.55	27	0.38					22.0	383
3/2	30	94	81	0.90	68	0.73	52	0.56	37	0.38						

\* On February 17, the plasma was strongly tinged with bile, less so on February 18, and not at all on February 24. The dog was quiet and drank a good deal of water on the two days following chloroform anesthesia. Food was withheld for five days previous to the anesthesia.

appearance of the dye from the blood stream was determined prior to the injury of the liver of the particular animal which was used for the experiment. The colorimeter readings represent the percentage concentration of the dye in the plasma as compared with the standard (0.0075 per cent). Since the plasma volumes from day to day under these experimental conditions are not constant, it is impossible to compare these readings directly. The effect of varying plasma volume may be eliminated by computing the ratios of the colorimetric readings at the two, four, eight and sixteen minute interval. If these ratios are plotted against the corresponding time intervals, a 'rate of dye elimination curve' will be obtained. This ratio decreases rapidly during the first intervals of time and less so at later time intervals.

Tables 1 to 4 show the effect of liver injury by chloroform anesthesia on the rate of elimination of the dye from the blood stream.

TABLE 1—*Percentage Concentration of Rose Bengal in the Blood Plasma Before and After Liver Injury by Chloroform Anesthesia*

Dog 22-40 (Adult Black and White Hound)\*

Colorimetric Readings and Values for R† at Intervals of												Weight, Pounds	Plasma Volume, Cc
Date, 1922	One Minute,	2 Minutes		4 Minutes		8 Minutes		16 Minutes		R			
	Per- cent- age	Per- cent- age	R	Per- cent- age	R	Per- cent- age	R	Per- cent- age	R				
3/ 7	99	88	0.89	69	0.70	38	0.39	22	0.22	24.5	405		
3/ 8	98	85	0.87	64	0.64	45	0.46	23	0.23	23.5	408		
3/ 8	Chloroform anesthesia 50 minutes												
3/ 9	104	100	0.97	89	0.86	83	0.80	70	0.67	22.8	386		
3/11	106	96	0.91	87	0.81	83	0.78	52	0.48	21.8	377		
3/14	94	80	0.85	72	0.76	48	0.50	36	0.38	21.8	425		
3/16	96	86	0.90	75	0.78	57	0.60	40	0.42	21.8	420		

\* The dog was isolated on March 5 and food was withheld until the experiment was completed. On March 9, the day following the anesthesia, the plasma was brightly colored with bile pigments, but less so on March 11 and only slightly so on March 14. The dog did not vomit or show signs of severe toxicity. He drank a copious amount of water.

† In this and other tables, R represents the ratio of the percentages of dye at any particular time to the percentage after the first minute interval. The dose of rose bengal equals 30 mg. for each injection.

In none of these cases did the injury prove fatal to the animal. It may be assumed that the animals were normal prior to the period of anesthesia. Nearly identical curves were obtained during the normal period of the same dog, and curves which are similar but which indicate a slightly different rate of dye elimination were found for other animals.

*Elimination of Dye Previous to Chloroform Anesthesia*—The colorimetric reading which was taken after the first minute interval varies in different dogs, since the concentration of dye is a function of the dilution of the dye in the total volume of blood which is in circulation. The higher the percentage concentration of the dye in the blood plasma with the same dose, the lower is the volume of plasma into which it is diluted. During the first minute after the injection, the dye is probably distributed fairly evenly through the circulation, if we assume

the chloroform anesthesia, and shows a decided lag. The high values for the ratios corresponding to the eight and sixteen minute time intervals subsequent to the injection of the dye show a marked contrast to the values which were obtained before the liver injury had been induced (Tables 1, 2, 3 and 4). This point is of particular significance, for, as has been pointed out previously, it indicates that the injury of the liver is intimately concerned with the elimination of the dye. Subsequent determinations which were made on the same dog on successive days after the liver injury had been induced show a gradual return to the normal type of curve, although in several instances the experiments were not prolonged over a period of time sufficient to lead to a complete recovery. Recovery from the effects of the liver injury took place in all four experiments, hence pathologic material confirming the extent of liver injury was not available, but

TABLE 5—*Percentage Concentration of Rose Bengal in the Blood Plasma before and After Liver Injury by Chloroform Anesthesia*

Dog 22-40

Date, 1922	Colorimetric Readings and Values for R at Intervals of										Weight, Pounds	Plasma Volume, Cc
	One Minute, Per- cent- age	2 Minutes		4 Minutes		8 Minutes		16 Minutes				
		Per cent age	R	Per cent age	R	Per cent age	R	Per cent age	R			
4/17	70			54	0.78	40	0.58	33	0.47	18.8	575	
4/19	64	60	0.94	51	0.80	36	0.58	30	0.47	19.0	625	
4/21	Chloroform anesthesia 90 minutes											
4/22	76	78	1.03	82	1.06	76	1.00	63	0.83	18.0	526	
4/23	93	107	1.16	94	1.02	89	0.96	87	0.94	17.5	432	
4/25	85	79	0.91	73	0.85	64	0.75	51	0.60	17.0	470	
4/26	77	73	0.95	66	0.85	54	0.70	48	0.63	16.0	517	
4/26	Dog killed under ether and necropsy performed										Dose of rose begal equals 30 mg for each injection	

the presence of bile pigments in the plasma indicated that definite injury had taken place. On account of lack of data, no attempt will be made in this paper to draw any correlation between the amount or extent of liver injury and the specific change in the curve of elimination that results from such injury. It is regretted that sufficient time was not available to obtain data on this point. Further work is necessary on many aspects of the problem.

Table 5 shows a more profound effect of chloroform anesthesia which was continued for a period of ninety minutes. The dog was sacrificed under ether in a moribund condition, and sections of the liver tissue showed a marked necrosis involving nearly all of the liver parenchyma. Yet even in this case there appears to be a tendency for the curve of elimination to return to normal.

Necropsy Notes (Table 5). Macroscopic examination showed a marked liver necrosis which was more marked in some areas, less so in others. The perilobular connective tissue was prominent and of a



that this dye behaves in a manner similar to the "vital red" which is used for the estimation of plasma volume. During this first minute there probably is some elimination of the dye, but it is probably small. A small interval of time for the even distribution of the dye through the circulation must be given, and some arbitrary time shortly after the injection for the first determination of dye concentration must be taken. The interval of one minute may introduce an inaccuracy with regard to the actual computed plasma volume, but the exact unit of time taken before the first sample of blood is withdrawn is immaterial, provided it is of short duration and constant for each curve that is made. Great care was exercised to ensure that each sample was drawn exactly on time. This was particularly necessary in the case of the one minute samples, since a few seconds' delay in the drawing of the sample will introduce a definite error.

It will be seen from the estimation of the fifth sample of blood, taken sixteen minutes after the injection of the dye, that the rose bengal has largely disappeared from the blood stream. (The colorimetric readings varied between 20 and 30 per cent.) This concentration of dye is about the lowest which can be estimated with any degree of accuracy in the Hellige colorimeter and denotes a very pale plasma.

*Elimination of Dye After a Period of Chloroform Anesthesia*—In these experiments, the animals were put under chloroform anesthesia for periods of time as indicated in the respective tables. The period of fasting previous to the day on which the animal was subjected to the chloroform anesthesia is given at the foot of each respective table. It is recognized that there is a definite relationship between the period of fasting and the extent of liver injury. The clinical effects of the anesthesia are indicated in each table, but these were not marked, and all of the animals recovered.

The first immediate effect of the liver injury by chloroform apparently is a fall in the plasma volume, since the concentration of dye in the plasma of the first sample was found to have increased. This is a constant finding in all of the experiments. All animals were sufficiently supplied with water, of which they freely partook after the period of chloroform anesthesia. The results therefore can hardly be explained on the basis of an insufficiency of water. It is possible that the increased thirst of the animals is the result of a decrease in the plasma volume. It is recognized that this dye is not as satisfactory for blood volume work as are the commonly used vital red dyes.

The second effect is a decided lag in the elimination of the dye, and the dye elimination curve becomes more nearly horizontal. The effect of chloroform anesthesia on the elimination of dye is not dependent on the elapse of a considerable interval of time after the anesthesia. The first estimation of dye elimination (Table 2) was made six hours after

dye, to which a few drops of the normal bile, collected during the period prior to the injection of the dye, were added. These readings were made in a Duboscq colorimeter, and considerable care was taken to ensure a perfect color match between the two solutions. This process was tedious and empirical, for it was impossible to calculate the exact amount of bile which must be added to the standard in order to secure the exact shade demanded by the specimen of colored bile which was obtained after the injection. During five hours of collection, 13 mg of the 30 mg which had been injected were recovered.

Following the injection of the dye, blood samples were withdrawn after one, two, four, eight and sixteen minutes, as in the previous experiments, and the percentage concentration of the dye in the plasma compared with the 0.0075 per cent solution of the dye was determined. The curve corresponds to the normal type of curve which was obtained in the other dogs. The amount of dye which was removed from the

TABLE 6—*The Quantitative Elimination of Rose Bengal in the Bile*

Time	Time Interval, Hours	Amount Collected, Cc	Dye Eliminated, Mg
*9:30 to 2:30	5	10.5	
2:30 to 3:30	1	4.0	1.864
3:30 to 4:30	1	4.5	5.201
4:30 to 5:30	1	4.15	4.016
5:30 to 6:30	1	0.75†	0.491
6:30 to 7:30	1	2.3	1.470

\* At 2:30, 30 milligrams of dye were injected.

† Most of the 5:30 to 6:30 sample was accidentally lost.

Total dye elimination equaled 13.042.

circulation by the taking of blood samples cannot possibly have had any material effect on the quantitative determinations in the bile.

At first sight it may appear that the dye itself possesses a cholagogue action, but when the many other factors which accompany this type of experiment and which may modify the secretion of bile are considered, one will hesitate to attribute the increased flow of bile to the action of the dye itself.

#### DISCUSSION

From the foregoing experiments, it appears that the elimination of rose bengal from the circulation is profoundly affected by injury of the liver, when this injury is induced through the agency of chloroform. With the experimental data at hand, it is impossible at this time to draw a correlation between the amount of liver injury and the extent of the change in the rate of elimination of the dye, and one would not be justified in claiming on the basis of the information thus far obtained that this method of experimentation will give any index of the activity of the liver in any one of its numerous and complicated functions.

pearly gray color. The liver parenchyma was gray and opaque. The gallbladder contained dye stained bile. The duodenum showed a considerable enteritis with reddish longitudinal streaks in the mucosa, which was denuded over small areas. There was a moderate amount of dye in the entire intestine. The blood of the animal was not clotted (necropsy performed some hours after death). There were 200 cc of serosanguineous fluid in both chest cavities. Microscopic examination of the liver showed an extensive liver necrosis involving most of the liver parenchyma, in some areas almost the entire liver lobule was destroyed, in others, the liver cells were swollen and granular.

*Comment*—From the data obtained in these experiments, the plasma volume can readily be calculated. If we consider that the mixing of the dye with the blood is complete after one minute, and that the amount of dye which is eliminated during that time is not yet sufficient to alter appreciably its concentration in the blood, and we find that the percentage concentration of the dye in the plasma, after the injection of 30 mg is, let us say, 58.7 per cent in terms of the 0.0075 per cent standard, it is easy to calculate the volume to which this dye has been diluted. The following equation may be deduced to express the plasma volume

$$\text{Plasma volume} = \frac{\text{Milligrams of dye injected} \times 10^5}{\text{Colorimeter reading} \times 75}$$

The plasma volume determinations are given in each table and are calculated with the aid of the foregoing formula.

#### EXPERIMENT ILLUSTRATING QUANTITATIVE ELIMINATION OF DYE IN BILE FOLLOWING INJECTION INTO CIRCULATION

An attempt was made to determine the rate of elimination of the dye through a bile fistula, following its injection into the circulation. A temporary fistula was established (Table 6), and the collection of normal bile was continued for five hours. During the first half hour following the operation no bile was secreted into the collecting bag, but during the subsequent four and one half hours 105 cc were collected. Thirty milligrams of the dye were injected into the jugular vein, and collections of bile were made hourly. It was noted that the bile flowing through the glass cannula was definitely tinged with the dye eighteen minutes after the injection had been made. In another dog the time of appearance of the dye in the bile at the body wall, where it was first visible, was eight minutes. Evidently the dye is rapidly eliminated from the blood, but it continued to appear in the bile of the dog for as long as five hours, which is the longest period of observation. The samples of bile which were collected hourly after the injection of the dye were compared with a standard solution of the

# THE BASAL METABOLISM DURING PREGNANCY AND THE PUERPERIUM \*

HOWARD F. ROOT, M.D., AND HESTER K. ROOT, A.B.  
BOSTON

The literature of normal pregnancy affords, so far as we are aware, no series of observations on the basal metabolism beginning with early pregnancy and continuing through the puerperium. Magnus-Levy,<sup>1</sup> in 1904, and Hasselbach,<sup>2</sup> in 1912, each reported a single case observed before conception and during pregnancy. Leo Zuntz,<sup>3</sup> in 1910, reported two cases with observations beginning in the fourth to the sixth months and continuing to delivery, and a third case in which observations were made in the sixth month only.

Magnus-Levy found both an absolute and relative increase in the oxygen consumption per unit of weight as early as the third month of pregnancy. Zuntz and other observers, however, found no increase in the oxygen consumption per kilogram, or, if any occurred, it appeared only late in the gestation period. Carpenter and Murlin,<sup>4</sup> in 1911, showed that the curve of total energy production of mother and child suffered no deflection at birth. They found that "the extra metabolism of the pregnant woman at the culmination of pregnancy, due in part to the accessory structures as well as to the fetus, is just equalled by the extra metabolism set up in the new-born child by exposure of its body to the outside world, and in the mother by the activity of the mammary glands," etc. The energy metabolism expressed per unit of weight of the pregnant woman was 7 per cent less than that of the same woman newly delivered, and about 4 per cent more than that of women in complete sexual rest. They concluded that the energy metabolism of the pregnant woman expressed per unit of surface is specifically higher than that of a woman in complete sexual rest, probably because of a higher metabolism in the uterus and because of a more rapid conduction of heat through the abdominal wall.

Baer<sup>5</sup> reported, in 1921, a series of forty-four patients with basal metabolism determinations at various periods during the last six weeks of pregnancy and the first eleven days postpartum. He compared the results obtained with the Aub and DuBois standards based on surface

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\* From the Nutrition Laboratory of the Carnegie Institution of Washington.

1 Magnus-Levy. *Ztschr. f. Geburtsh. u. Gynak.* **52** 116, 1904.

2 Hasselbach. *Skand. Arch. f. Physiol.* **27** 1, 1912.

3 Zuntz, L. *Arch. f. Gynak.* **90** 452, 1910.

4 Carpenter, T. M., and Murlin, J. R. *The Energy Metabolism of Mother and Child Just Before and Just After Birth*, *Arch. Int. Med.* **7** 184 (Feb.) 1911.

5 Baer, J. L. *Am. J. Obst. & Gynec.* **2** 1, 1921.

From a study of the elimination of rose bengal from the blood streams of a large number of cases, it should be possible to determine the time limits which are required to reduce the concentration of dye in the blood stream to an indefinite amount. A lag in the elimination of dye from the blood stream can then be determined. This may give an index of the liver injury, or, if the term be permitted, of liver function.

#### CONCLUSIONS

Rose bengal, when injected into the circulation of normal dogs, at a dosage of about 20 mg per 20 pounds (9.7 kg) of body weight, remains in the blood stream for at least sixteen minutes.

Examination of samples of blood which were withdrawn from the circulation at definite specified intervals after the injection of the dye shows that there is a constant rate of elimination of the dye. The percentage concentration of the dye in the plasma as determined at definite time intervals may be tabulated and a "normal" curve of elimination of the dye may be obtained.

Under certain conditions of liver injury, such as may be induced by chloroform, the curve of dye elimination is markedly influenced and indicates a slower elimination of dye.

hockey, etc., for years without any evidence of cardiac weakness. During pregnancy she was able to carry on her usual activities with practically no limitation. Physical examination revealed no evidence of cardiac damage. The increase in the vital capacity is itself good evidence of the normal cardiac condition.

Labor pains were first felt about 1 a. m. on July 31. During one and one-half hours in the first stage, self-administered nitrous oxid relieved the intensity of the pains, and in the second stage under ether anesthesia, delivery was hastened by the application of low forceps by Dr. R. C. Cochrane. Birth of a girl baby occurred at 11 30 a. m., July 31, after ten and one half hours' labor. After a hospital stay of two weeks and three days, she returned to her home. During the first two weeks of the puerperium she was in bed, then followed two weeks of gradually increasing activity, and the resumption of nearly normal activity at the end of a month.

#### METHODS

A Benedict portable respiration apparatus was used, and the observations were made approximately at two weeks intervals at the patient's home, with the exception of the first two following delivery, which were made in the New England Baptist Hospital. During the last three weeks of pregnancy, observations were made weekly. The same apparatus was used throughout the entire period of observation. The usual precautions as to the omission of food for twelve hours and absolute rest in bed for at least one-half hour preceding tests were observed.

On the night before a test day, the subject's weight was taken at 10 30 p. m., and she went to bed at about 10 45 p. m. She arose at 6 30 a. m. to urinate and to be weighed and then returned to bed, often sleeping until the arrival of the operator at 8 a. m. While in the hospital, the determinations were made when she was still confined to bed, and hence no activity intervened between the night's rest and the test, with the exception of such activity as was involved in nursing the baby at 6 a. m. Careful notes were made as to the rare instances of nervousness on the part of the subject and of any possible cause for disturbance. During the later months fetal movements occurring during the periods were recorded. The subject reported that at almost all hours of the day slight movements could be felt if her attention was not focused on other matters, hence only unusual movements were recorded. On one occasion, such movements occurred following the first period, and consequently the second period was delayed until the activity had subsided.

So far as extraneous movements on the part of the subject, such as turning on the side, raising the hand, or changing the position of the

area A total of 127 determinations were made, of which fifty-two were prepartum and seventy-five postpartum From these figures expressed in percentage plus or minus, he constructed a chart showing on the average an increase from  $+26$  per cent in the thirty-sixth week to  $+33$  per cent in the fortieth week of pregnancy, and a decline from  $+15$  per cent on the third day postpartum to  $+14$  per cent on the eleventh day No individual records are shown He also suggested the use of basal metabolism determinations in diagnosing fetal death or the presence of twins

Cornell,<sup>6</sup> in a more recent study of eighty-four cases, found the basal metabolism subject to many influences and the results of no value in practical obstetrics

The results of Baer and Cornell were obtained on a series of patients, including many pathologic cases Furthermore, the average number of observations per patient in both series is less than three, including prepartum and postpartum periods Lack of control of psychologic factors is admitted by Cornell The need for a long series of observations on individual patients during pregnancy and the puerperium is clearly indicated

This study of a single subject is here reported because observations beginning in the fifteenth week of pregnancy have been continued at short intervals until the eighth week after delivery in the case of an extraordinarily normal pregnancy in which psychologic and physical factors exerting an untoward influence on the determinations were not present So far as we are aware, no series of observations on normal pregnancy comparable in frequency and length of period covered have been reported previously

#### SUBJECT

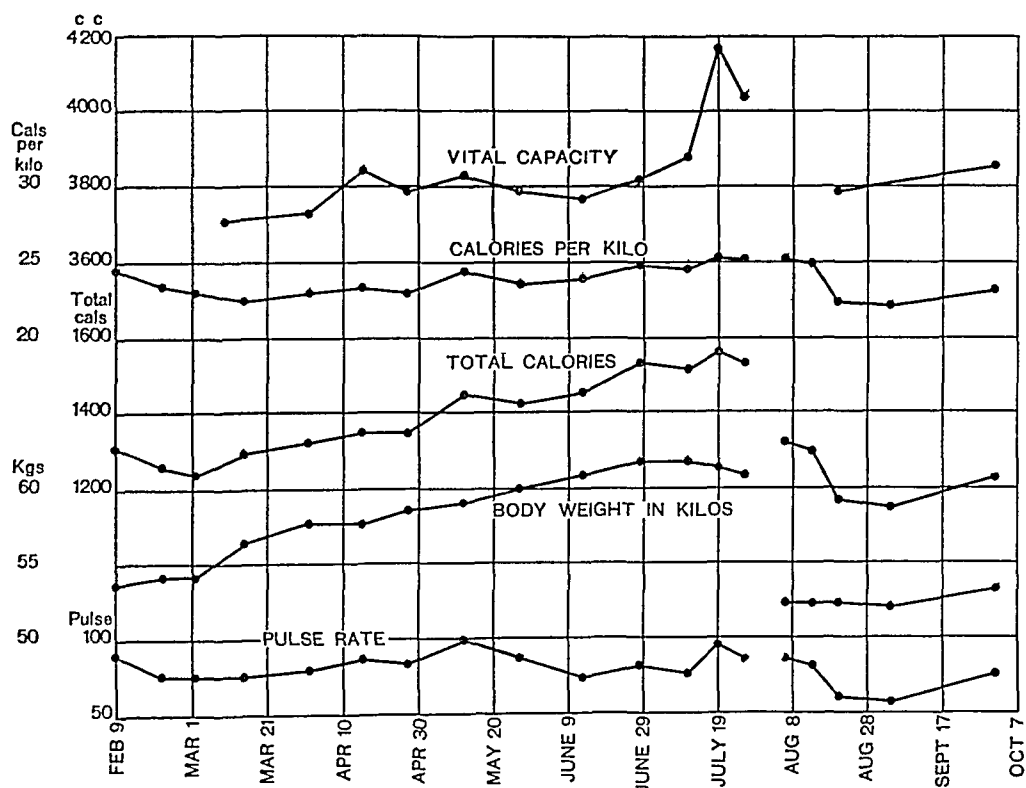
The subject of these observations was a normal primipara, aged 29 years, four and one-half months, at the beginning of pregnancy The date of the last menstruation was Oct 22, 1921 Morning nausea and vomiting occurred during the third month but not thereafter No febrile complications arose at any time during pregnancy or the puerperium Indeed, the buccal temperature never exceeded 99 F even on the day of delivery Edema of the ankles was present one day during the second month and was constantly present during the last three months, though varying in amount Thus, on rising in the morning little or no pitting edema could be detected, although a considerable degree of edema was present in the evening The high pulse rate deserves some comment Frequent examinations over a period of from eight to ten years had always shown an unusually high rate from 85 to 90 She had enjoyed moderately strenuous athletics, swimming, canoeing,

TABLE 1—*Computed Basal Metabolism\**

Date, 1922	Oxygen per Minute, O c	Pulse	Body Weight (Nude), Kg	Computed Calories per 24 Hours	Deviation from H and B † Standard, Percentage	Calories per Kg per 24 Hours	Increase in Calories per 24 Hours Over Average of Feb 9 to March 2 Percentage
Feb 9	188	90	53.6	1,308	-1.5	24.4	
Feb 21	181	76	54.1	1,260	-5.4	23.3	
Mar 2	179	76	54.1	1,240	-7.1	22.9	
Mar 15	187	76	56.4	1,297	-4.2	22.4	+ 2.2
April 1	190	80	57.7	1,321	-3.3	22.9	+ 4.1
April 15	194	87	57.7	1,347	-1.3	23.3	+ 6.1
April 27	194	84	58.6	1,347	-1.6	22.9	+ 6.1
May 12	208	99	59.1	1,448	+5.2	24.4	+14.1
May 27	204	87	60.0	1,421	+2.6	23.6	+12.0
June 13	209	74	60.9	1,454	+4.4	23.9	+14.6
June 28	221	82	61.8	1,530	+9.5	24.8	+20.6
July 11	218	77	61.8	1,514	+8.2	24.6	+19.3
July 19	225	96	61.4	1,561	+12.1	25.3	+23.0
July 26	221	87	60.9	1,530	+10.1	25.2	+20.6
July 31 delivery							
Aug 6	190	87	52.3	1,321	+0.7	25.2	+ 4.1
Aug 13	187	82	52.3	1,301	-0.9	24.9	+ 2.5
Aug 20	168	61	52.3	1,167	-11.5	22.3	- 8.0
Sept 3	165	58	52.0	1,147	-12.9	22.1	- 9.6
Oct 1	177	76	53.2	1,227	-7.5	23.0	- 3.3

\* All the metabolism figures reported in this paper were based on the revised methods of calculation resulting from a critical test by Dr T. M. Carpenter of the Nutrition Laboratory of this portable apparatus (by burning known amounts of alcohol) and represent most accurate measurements of the oxygen consumption.

† "H and B" is an abbreviation for Harris and Benedict, Carnegie Institution, Washington, Pub No 279, 1919, Tables 3 and 4, pp 260 et seq.



Curves for pulse rate per minute, body weight, basal heat production per twenty-four hours and per kilogram per twenty-four hours, and vital capacity from the fifteenth week of pregnancy until the eighth week after delivery (July 31, 1922)



feet, are concerned, it may be definitely stated that none occurred during the metabolism tests. The reasons for such cooperation were first, the extraordinary composure and self-control of the subject, second, the exercise of great care in making the subject comfortable before beginning experiments, and third, the intelligent understanding on the part of the subject of the nature of the test being carried out.

Observations were always made in three ten minute periods. Tests for leakage of the apparatus and connection with the mouth were made during each period according to a new technic. Such tests were invariably negative and demonstrated the absence of a leak.

#### DATA

In Table 1 are given the data of the metabolism experiments which may be referred to, and in Figure 1 are given the curves for the metabolism, body weight, pulse rate, and vital capacity.

We first call attention to column 5, Table 1, showing the total basal calories per twenty-four hours. The average of the first three determinations was 1,269 calories, with which, in the absence of observations preceding pregnancy, we must compare the metabolism at later dates. The total computed twenty-four hour basal metabolism steadily increased until on July 19 the computed metabolism was 23 per cent greater than it was five months previously. This extraordinary increase in basal metabolism was accompanied by an increase in weight of but 14 per cent. It is clear, therefore, that the specific metabolism of the newly gained tissue must have been considerably higher per kilogram than that of the subject before the increase in weight occurred.

This increase in metabolism is out of all proportion to the increase in metabolism which would occur in a normal woman of the same age and height with a similar gain in weight. Thus, the normal woman, according to the table of Harris and Benedict, of the same age and height would gain in metabolism only 5 per cent with a similar gain in weight. According to the prediction tables of Aub and Du Bois, the gain in metabolism under the same conditions would be 5 per cent. It is clear, therefore, that the gain in basal metabolism of the pregnant woman, as she gains in weight, is at a different rate, at least in the later months of pregnancy, from that shown by the normal woman by the standard prediction tables.

Following delivery, the patient's weight remained fairly constant, yet marked changes in the basal metabolic rate were observed. The total basal calories fell rapidly during the first three weeks after delivery to the lowest level observed at any time during the eight months, 9.6 per cent below the level during the third month of pregnancy.

We regard this comparison of the patient herself against herself at different periods as of greater importance than a comparison of the

The discrepancies were noted at the time, and every effort made to find an explanation. By a new technic a test for tightness of the apparatus was made during the progress of every period, and in both these instances no evidence of leakage could be found. Further tests for leakage were made at the end of these periods, without result. The same stop-watch was used throughout. In short, we have no reason to suspect the apparatus or the timing of the periods. The subject denied experiencing any discomfort or any unusual sensations. No unusual fetal movements were felt. It appears, therefore, that the occurrence of brief periods of greatly increased metabolism during the latter part of pregnancy must be accepted until definite proof to the contrary is produced.

The interpretation of such variations would seem to depend chiefly on the assumption that great variations in fetal activity may occur without corresponding disturbance of the mother. The significance of kymograph records purporting to give evidence of the character of

TABLE 2—*Variations in Consumption of Oxygen*

Date	Period	Oxygen Consumption, C c	Pulse	Time, a m
June 28	I	220	85	8 17
	II	242	88	8 39
	III	221	78	8 57
July 26	I	223	90	8 25
	II	279	97	8 42
	III	218	83	9 02

fetal movements has been questioned by such authorities as Williams.<sup>8</sup> There seems to be no definite knowledge as to the nature and metabolic influence of fetal movements. However, no better explanation for these figures is at present available. These periods, however, were not regarded as basal and accordingly were not used in the averages.

Three other factors possibly influencing the basal metabolism in pregnancy may be mentioned. The first of these is seasonal variation. The early months of pregnancy occurred in the winter, whereas the later months and the puerperium occurred in midsummer. No evidence of any seasonal influence is obtainable from the data.

Hasselbalch<sup>9</sup> found slight acidosis present during the last weeks of pregnancy in his subject. It is possible that slight acidosis, as shown by lowered plasma carbon dioxide combining power may accelerate the basal metabolism.

Hypertrophy of the thyroid is frequently observed during pregnancy, and many writers have spoken of a compensatory hyperactivity

<sup>8</sup> Williams, J. W. *Obstetrics*, New York, D. Appleton & Co., 1922, p. 163.

<sup>9</sup> Hasselbalch. *Skand. Arch. f. Physiol.* **27** 1, 1912.

pregnant woman at any given stage with a nonpregnant, standard, normal woman of like age and weight. However, such comparison is of some interest, and, accordingly, under Column 6 in Table 1 are given the percentage deviations from the standard prediction of Harris and Benedict for normal women of the same age, height and weight. It may be stated that the predictions of Aub and Du Bois closely paralleled those of the Harris and Benedict tables at all stages, showing an average difference of but forty-seven calories. Accordingly, the percentage deviations from their predictions are but slightly different.

These figures for percentages plus or minus standard predictions stand in strong contrast with the results obtained by Baer. His forty-four patients averaged from +26 per cent in the thirty-sixth week to +33 per cent in the fortieth week, using the Aub and DuBois standard for comparison. He made, however, only fifty-two determinations on forty-four patients from the Michael Reese Maternity Clinic, of whom eighteen were primiparae. It was difficult under these circumstances to eliminate psychologic and other factors, which might produce considerable increases in the metabolic rate.

It is pertinent at this point to comment on certain factors affecting the metabolism in pregnancy. Diurnal variation in the basal metabolism of a man undergoing a prolonged fast has previously been reported from this laboratory.<sup>7</sup> A similar lowering of the metabolism was observed on one occasion during these observations. On March 15, the subject slept during the third period, and her oxygen consumption decreased by 9 per cent during this period. Since our object was to secure data comparable with standards which have been derived from observations on the waking state, this period was not used in making up our average. However, it agrees with other observations from this laboratory in indicating a lowering of approximately 10 per cent in the metabolism during sleep, and suggests that only during sleep can the maximum relaxation required for a true "basal" determination be secured.

Another important factor affecting the metabolic rate, especially in primiparae, is the degree of mental relaxation. On February 9, both the pulse rate and the oxygen consumption were higher than for the next three determinations. The subject denied any feeling of nervousness, and appeared quite comfortable, but it is probable that the newness of the experience was disturbing, nevertheless. Single observations under these circumstances are open to doubt.

During the last six weeks of pregnancy, evidence was obtained of the existence of factors influencing the metabolism much more markedly. On June 28 and July 26, the second of three periods each gave figures for oxygen consumption much greater than the first and third.

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7 Benedict, F. G. Carnegie Inst. Wash. Pub., No. 203, 1915, p. 337.

Approximately 2 kg remain unaccounted for, which probably consisted of edema. The metabolically active tissue lost at delivery consists of the child, the placenta and that portion of the uterus which is lost during involution. The approximate weight of these tissues was 5.6 kg. The difference between the twenty-four hour basal metabolism five days before delivery and six days after was 209 calories. The metabolic rate for baby, placenta, and uterus just before delivery would accordingly seem to have been about 37 calories per kilogram. It is of some interest to compare this estimate with the observed minimum metabolism of new-born infants reported by Benedict and Talbot,<sup>10</sup> who found an average of 42 calories per kilogram as the minimum metabolism of 105 new-born infants.

In the following tables are given such figures for the oxygen consumption reported by other writers as were found.

TABLE 4—Oxygen Consumption per Kilogram of Body Weight Per Minute<sup>1</sup>

Condition	Authors' Case, O c	Magnus Levy, O c	Zuntz			Carpenter-Murlin			Hasselbalch, O c
			(A) O c	(B) O c	(C) O c	(1) O c	(2) O c	(3) O c	
Normal		2.79	3.47	3.50	3.75				
During 3d mo		2.88							
During 4th mo	3.15	2.92			3.72				
During 5th mo	3.30	3.16		3.65	3.54				
During 6th mo	3.33	3.14	3.88	3.52					
During 7th mo	3.42	3.10							
During 8th mo	3.42	3.20		3.92	3.45				
During 9th mo	3.59	3.33		3.75	3.47	3.4	3.9	3.4	2.93
Weight (nude) before delivery, kg	60.9	115.1		58.04	67.8	63.0	58.0	68.2	76.3
Puerperium—									
1st week	3.61								
2d week	3.58						4.12	3.34	
3d week	3.22					3.46			
4th week	3.18								2.85
5th week									2.70
8th week	3.32								2.96

\* All values are computed to 0°C and 760 mm and previous to delivery are averages obtained from observations on two or more days.

The only patient who did not show a higher oxygen consumption in the later months of pregnancy than in earlier months was Zuntz's Patient C. She had acute pyelitis with fever in the fifth month and thereafter gained much weight. He calculated that she gained 7 kg in fat alone. His Patient A actually weighed less at term than before conception. This strongly suggests some abnormality and perhaps invalidates the comparison of the oxygen consumption in the middle and at the end of pregnancy.

The influence of obesity on the oxygen consumption per kilogram of body weight is well shown by the figures given above. Thus, in the ninth month, the lowest oxygen consumption is found in the case of

<sup>10</sup> Benedict, F. G., and Talbot, F. B. Carnegie Institution Washington Pub. No. 233, 1915, p. 99.

of the thyroid at the time. Neither hypertrophy of the thyroid nor any constant increase in pulse rate appeared in this subject, and consequently no objective evidence can be brought forward indicating any special influence on the part of the thyroid.

The curve of calories per kilogram is an instructive one. From February 9 until April 27 it is fairly constant, but from April 27 until July 26 it shows a striking rise from 22.9 to 25.2 calories per kilogram. Fluctuations in body weight during this time were greater than during the early part of pregnancy. Thus the average difference in weight between weights taken at 10 p. m. and 6.30 a. m. from July 20 to July 26 was 2.6 pounds (7257.4 gm.), whereas in February the average difference in these weights for a corresponding period was 1 pound (4535.9 gm.). The warmer weather, disappearance of edema during the night, and the increased metabolism no doubt influenced this fact. It should be said, however, that practically all edema of the extremities had disappeared in the morning when the metabolism tests were made, and the curve of weights taken at this time is an extraordinarily regular one.

During the first two weeks of puerperium, the heat production fell slightly, to 24.9 calories per kilogram, and at the end of the third week, the rate was 22.3 calories per kilogram.

In any consideration of the heat production per kilogram during pregnancy, gain in adipose tissue is important. Of Zuntz's three patients, two gained weight independently of the products of conception. Magnus-Levy's patient was a giantess who apparently did not gain in adiposity. It is not clear from the paper of Carpenter and Murlin whether their three patients had gained adipose tissue during pregnancy or not. Our subject weighed, one week after delivery, 1.3 kg. more than she did before conception. Such a difference may well be accounted for as due to increased mammary and uterine tissue, and certainly does not indicate such a gain in adipose tissue as would influence the heat production per kilogram. The difference in weight between that of five days before delivery and one week after was 8.6 kg., which may be compared with an average loss of 7.257 kg. between the thirty-ninth or fortieth week and the third day postpartum reported by Baer. This difference may be analyzed as follows:

TABLE 3—*Elements Causing Increase in Weight Before Delivery*

Baby	Kg
Placenta	3.8
Liquor amnii	0.8 (approximately)
Uterine increase	1.0 (approximately)
	1.0 (approximately)
Total	6.6

aids for pregnant women should be established. In the hope that our results may be more useful to other observers we submit Table 5 of physical measurements.

Before commenting on these results, some explanation of the method of measurement is necessary. Height was taken in stocking feet. The trunk length is the measurement recommended by Dreyer. The subject sat on a level surface with the back against a measuring rod. With the back of the knuckles on the floor the body was bent forward and raised and the sacrum thrust against the measuring rod. Then with the hands in the lap and the body erect, the height to the vertex was taken. Chest circumference was measured just below the mammary tissue and with the chest at rest, that is, neither at maximum inspiration or expiration. The interacromial diameter was taken by means of obstetric calipers and represents the distance between the tips of the acromion processes with the patient standing erect, the arms hanging at the sides. The anteroposterior chest diameter was also taken with obstetric calipers and represents the distance in the horizontal

TABLE 5—*Physical Measurements*

	March 10, 1922	May 21, 1922	Oct 5, 1922
Lengths—Height	162.4	162.4	162.7
Trunk	84.8	81.8	84.4
Diameters—Interacromial		34.0	35.4
Chest, anteroposterior		19.5	18.2
Chest, internal		26.0	25.0
Intercostal		28.5	28.6
Circumference—Chest	75.5	77.0	73.5
Weight	55.5	60.0	53.1

plane from the lower border of the sternum to the opposite spinous process. The lateral chest diameter was the maximum diameter between opposite sixth ribs taken in midaxillary line. These two chest diameters were taken with the chest at rest and are bony measurements, the points of the calipers being approximated to bony surfaces as nearly as possible. The intercostal diameter was also taken with obstetric calipers and represents the maximum diameter between the outer lips of the iliac crest.

One purpose in taking these measurements was to determine whether measurements which have been recommended as standards for weight prediction would vary with the change of weight during pregnancy. It is obvious that the measurements of length, which are essentially bony measurements, show no variation. Slight variation appears in the diameters, with the exception of the intercostal diameter. The correlation between the intercostal diameter and normal weight should be studied with a view to determining its usefulness in assessing normal weight. The largest variation appears in the chest circumference, which almost parallels the changes in weight. The close rela-

the patient of Magnus-Levy, whose weight at this time was 115.1 kg. The highest oxygen consumption per kilogram per minute is seen in the case of the second patient of Carpenter and Murlin, whose body weight was the least of all cases here shown.

Our observations do not confirm those of Carpenter and Murlin in finding a higher energy production per kilogram during the puerperium than in the ninth month of pregnancy. The first impression gained by examining the first column of Table 4 is that the oxygen consumption at the end of the first week of the puerperium is greater than that during the ninth month. However, this figure, 3.64, was obtained on a single date, whereas the figure 3.59 represents the average of four different observations. On consulting Table 1, it is clear that the highest metabolism per kilogram of body weight occurred on the eleventh day before delivery. If the two highest figures during the puerperium are compared with the last two observations during pregnancy, again the higher basal rate is observed during pregnancy. The average calories per kilogram per hour for the four weeks preceding delivery was 1.08 as against 1.03 for the four weeks after delivery. In all three of their patients, a decided increase in the calories per hour per kilogram occurred during the puerperium as compared with observations made from one day to three weeks preceding delivery. The average increase was 7 per cent. They suggested that the process of involution set free decomposition products which stimulated the general heat production. Hyperactivity of the sweat glands and the activity of the mammary glands were also considered as explanations. It may be pointed out, however, that although no fever was present at the time of metabolism determinations the clinical charts of these patients show in each case afternoon temperatures, on several occasions taken by mouth, ranging from 99 to 100 F. While these temperatures are not considered clinically pathologic, they represent a considerable variation from the temperature curve of the present subject which did not rise above 99 F at any time during the puerperium. During the first two weeks the basal metabolism showed only a slight downward tendency, but by the third week it had fallen to a point lower than at any time during pregnancy, both total and per kilogram. This low level was found at the end of the fourth week, but eight weeks after delivery, with a slight increase in body weight, the oxygen consumption rose somewhat, possibly in part due to a considerable increase in diet on the part of the subject.

#### PHYSICAL MEASUREMENTS

We have called attention to the striking difference between the gain in basal metabolism by the pregnant woman in the later months of pregnancy and the gain in metabolism with a similar gain in weight on the part of the nonpregnant woman. It is important that metabolism stand-

have some evidence of an increase in chest volume from the chest measurements. Thus the circumference on March 10 was 75.5 cm, on May 24 it was 77.0 cm, and on October 5, two months after delivery, it was 73.5 cm. The chest diameters were also greater on May 24 than on October 5. Unfortunately, we have no chest measurements taken at the time of the highest vital capacity readings. A further suggestion as to the relation of an increased chest volume as an explanation of this high vital capacity comes from the fact that the greatest increase in vital capacity occurred during the period when the uterus descends somewhat into the pelvis, presumably releasing the upward pressure and allowing freer descent of the diaphragm.

An interesting possibility is based on the assumption that the vital capacity measures cardiac power and efficiency. It may be that during the last few weeks of a normal pregnancy the heart truly gathers its forces in preparation for the supreme test of labor, and that this increase in vital capacity is an evidence of this adaptive mechanism.

Hasselbalch found the vital capacity slightly greater in the last month of pregnancy than thereafter, and considered this fact due to the more complete emptying of the lungs and less residual air. However, the changes in lung volume were not great.

A comparison of the observed vital capacity with the standard predictions of West, Peabody, and Dreyer shows striking differences. The range of the standards is from 3,050 cc to 3,497 cc for the measurements of the subject observed on March 10, Dreyer's prediction from the chest circumference being much nearer to the observed 3,710 cc. When the entire series of observations is compared with the predictions, again the Dreyer prediction from chest circumference seems the closest. It follows from the fact that weight and chest circumference have a high degree of correlation that the vital capacity predicted from the weight should vary somewhat as that predicted from the chest, and, in fact, Dreyer's prediction from weight does run parallel to the chest predictions.

#### SUMMARY

The course of the basal metabolism from the fifteenth week of pregnancy to the eighth week after delivery is reported in the case of a primipara in whom pregnancy was uncomplicated by gain in adipose tissue or disease of any sort. The basal metabolic rate during the fourth month was essentially that predicted by the standard for non-pregnant women of the same age, height and weight. From this time, a steady increase in the total calories per twenty-four hours was observed until eleven days before delivery, when the total basal metabolism was 23 per cent greater than that during the fourth month. This increase in metabolism is out of all proportion to the increase in basal metabolism shown by standard prediction tables for normal



tion between the chest circumference and body weight, both in normal persons and in diabetic patients who are much overweight, has recently been shown by Gray and Root<sup>11</sup> and Root and Miles<sup>12</sup> It is of some interest that this measurement also reflects the changes in body weight during pregnancy No doubt the upward pressure of the pregnant uterus causes some flaring outward of the lower ribs, in which case the increase in diameter may be considered entirely mechanical rather than actually due to increase of soft tissues outside the ribs

#### VITAL CAPACITY

Measurements were taken with the Benedict portable respiration apparatus with the subject standing robed in a loose gown Five readings were taken, and the highest of the five recorded Usually the third was the highest

TABLE 6—*Observed Vital Capacity Compared With Three Standards*

Date	Observed	Room Tempera- ture, C	West*	Pea body†	Dreyer‡ Prediction from		
					Trunk	Weight	Chest
March 10, 1922	3,710		3,160	3,050	3,299	3,305	3,477
April 1, 1922	3,731	22.0	3,250	3,050		3,376	
April 15, 1922	3,841	19.8	3,250	3,050		3,376	
April 27, 1922	3,790	20.0	3,260	3,050		3,415	
May 12, 1922	3,833	18.6	3,274	3,050		3,435	
May 27, 1922	3,790	20.2	3,286	3,050	3,299	3,473	3,675
June 13, 1922	3,770	19.1	3,306	3,050		3,511	
June 28, 1922	3,820	22.5	3,334	3,050		3,548	
July 11, 1922	3,890	21.7	3,334	3,070		3,548	
July 19, 1922	4,170	27.0	3,320	3,050		3,532	
July 26, 1922	4,040	21.1	3,306	3,050		3,511	
Aug 20, 1922	3,790	22.0	3,100	3,050		3,147	
Oct 1, 1922	3,856	22.8	3,120	3,050	3,245	3,184	3,267

\* West, H. F. Clinical Studies on the Respiration. VI. A Comparison of Various Standards for the Normal Vital Capacity of the Lungs, *Arch Int Med* **25**: 306 (March) 1920.  
 † Peabody, F. W., and Wentworth, J. A. Clinical Studies of the Respiration, IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, *Arch Int Med* **20**: 443 (sept) 1917.

‡ Dreyer, G., and Hanson, G. F. The Assessment of Physical Fitness, New York, Paul B. Hoeber, 1921, p. 52 et seq.

The subject always exhibited a higher vital capacity than the standard shown, even two months after delivery. The latter fact eliminates pregnancy as the sole cause for her hypernormal vital capacity and is in accord with the observation that persons with athletic training may have exceptionally high vital capacity.

The vital capacity curve during pregnancy was most striking. A slight but definite upward trend is apparent from the third to the eighth month, with a marked increase during the last month. That this was not a practice effect is indicated by the fall to the earliest level on August 20, three weeks after delivery. The reasons for this decided increase during the last month of pregnancy are not entirely clear. We

11 Gray and Root. *Boston M. & S. J.* **185**: 28, 1921.

12 Root and Miles. *J. Metab. Res.* **2**: 173, 1922.

# TOXIC NEPHRITIS IN PYLORIC AND DUODENAL OBSTRUCTION

RENAL INSUFFICIENCY COMPLICATING GASTRIC TETANY \*

GEORGE E BROWN, M D, GEORGE B EUSTERMAN, M D,  
HOWARD R HARTMAN, M D

AND

LEONARD G ROWNTREE, M D

ROCHESTER, MINN

The clinical, pathologic and biochemical changes resulting from obstruction in the upper intestinal tract have been carefully studied by a number of investigators. It is known that a marked or complete pyloric or duodenal obstruction results in severe toxemia or death. The associated increased nerve irritability and the development of a syndrome usually designated gastric tetany have long been recognized. Experimental work along these lines has been concerned chiefly with the nature of the toxic agent, with the changes in blood chemistry, and with the mechanism involved in the production of gastric tetany. The cause of death in this group of cases also has received much attention. Various hypotheses have been advanced, based on experimental studies and on theoretic considerations, but we believe that the associated renal lesion has not yet received sufficient recognition or consideration.

Clinically it has been observed that the body reacts differently to intestinal obstruction, depending on certain factors, such as (1) the location of the obstruction, (2) the degree of the obstruction, (3) the acuteness of the process, and (4) individual susceptibility to the specific toxin involved as expressed clinically by increased nerve irritability, spasmophilia, vomiting, etc. It is possible also that the kidney may vary in susceptibility to injury, particularly in the presence of an existing disease.

We are attempting to show here that serious renal injury exists in many cases of duodenal and pyloric obstruction, particularly in cases exhibiting evidence of tetany. We are not attempting to controvert the importance of increased tissue catabolism in the production of a high level of blood urea, but wish to emphasize the importance of the renal lesion. The toxic injury sustained by the kidney is of grave consequence and is characterized by (1) albuminuria and cylinduria, (2) marked functional impairment of the kidneys, associated with marked increase of total nonprotein nitrogen, of creatinin and of urea

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\* From the Division of Medicine, Mayo Clinic

women with a corresponding gain in weight. The gain in basal metabolism expressed as calories per kilogram from the fourth month of pregnancy to the eleventh day before delivery was 7.6 per cent. Following delivery, although the subject's weight remained nearly stationary, the basal metabolism fell gradually to a point 9.6 per cent lower than the rate observed during the fourth month of pregnancy.

The high metabolic rate during the last month of pregnancy only partially reflects the much higher metabolic rate of the fetus per unit of weight since the maternal weight is made up in part of inactive tissues such as edema and the fluid contained in the amnion. It appears from our computations that the metabolism of the fetus at term was approximately 37 calories per kilogram, whereas the basal metabolism of the mother was 23.5 calories per kilogram during the fourth month of pregnancy, and 22.1 calories per kilogram one month after delivery.

The vital capacity increased steadily from the fifth month onward with a marked rise in the last months of pregnancy.

#### CONCLUSIONS

1. A marked increase in the basal metabolism both in total twenty-four hour calories and in the calories per unit of weight occurs during the later months of pregnancy.

2. The heat production per unit of weight falls gradually during the first three weeks after delivery to a level lower than that observed during the fourth month of pregnancy.

3. Standards of basal metabolism for use in practical obstetrics should be developed by the study of normal pregnant women, and a comparison of the basal metabolism of pregnant women should not be made with standards of basal metabolism for nonpregnant women.

that bacteria are essential for the production of the characteristic toxic substances. The splitting up of proteins produces a substance which causes the characteristic toxemia. Recently, Gerard<sup>5</sup> has suggested that histamin may be the toxic agent. Abel and his collaborators are at present investigating histamin and histamin containing albuminoses, and in all probability their work will shed some light on the nature of the toxic agent involved.

Werelius,<sup>6</sup> as the result of his work, questions the conclusions of Whipple and his associates and attempts to involve insufficiency of the liver as an etiologic factor in death following high intestinal obstruction. He questions whether the absorption of toxic products from the intestinal mucosa plays any part in causing death. He emphasizes the presence of white bile in the duodenum, of a lowered blood sugar level and an increased blood urea content as possible results of hepatic insufficiency.<sup>7</sup> Strangely, he failed to find an increase of carbon-dioxid carrying capacity of the blood.

The blood chemistry in high intestinal obstruction reveals much of interest. Wilson, Stearns and Janney<sup>8</sup> were the first to call attention to the presence of alkalosis in parathyroidal tetany. McCallum<sup>9</sup> and his associates and McCann<sup>10</sup> studied the relationship of tetany to pyloric closure and found that the plasma chlorids dropped sharply in this condition, that the alkaline reserve was definitely increased, and that the electrical reactions were heightened. The alveolar carbon dioxid was markedly increased, showing that there was no carbon dioxid retention in the blood. Their animals developed twitchings, convulsions and coma prior to death. It is difficult to determine whether the condition induced by these writers corresponds to that seen in this group of patients, owing to the lack of clinical details in their report. They noted that with the constant loss of gastric juice and its hydrochloric acid there ensues a decrease of the chlorids of

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5 Gerard, R W. The Lethal Agent in Acute Intestinal Obstruction, *J A M A* **79** 1581-1584 (Nov 4) 1922

6 Werelius, A. Is Death in High Intestinal Obstruction Due to Liver Insufficiency? *J A M A* **79** 535-539 (Aug 12) 1922

7 In hepatic insufficiency the urea nitrogen constitutes, as a rule, a decreased, rather than an increased percentage of the total nonprotein nitrogen. His explanation of the increased urea concentration does not seem convincing.

8 Wilson, D W, Stearns, T, and Janney, J H, Jr. The Excretion of the Acids and Ammonia After Parathyroidectomy, *J Bio Chem* **23** 123-137 1915

9 MacCallum, W G, Lintz, H, Vermilye, H N, Leggett, T H, and Boas, E. The Effect of Pyloric Obstruction in Relation to Gastric Tetany, *Bull Johns Hopkins Hosp* **31** 1-7, 1920

10 McCann, W S. A Study of the Carbon Dioxide Combining Power of the Blood Plasma in Experimental Tetany, *J Biol Chem* **35** 553-563, 1918. A note on the Use of Ammonium Chloride in Gastric Tetany, *Proc Soc Exper Biol & Med* **19** 393-394, 1922

in the blood, and a definite decrease in phenolsulphonephthalein excretion, (3) a clinical syndrome due, in part at least, to renal insufficiency, and (4) a well-defined pathologic picture of toxic nephritis

#### CLINICAL OBSERVATIONS AND EXPERIMENTAL DATA RELATIVE TO HIGH INTESTINAL OBSTRUCTION

Intestinal obstruction is less serious and runs a more chronic course with symptoms less acute, the lower the obstruction. The higher the block in the gastro-intestinal tract, the more fulminating are the symptoms and the more serious is the prognosis.

Among the hypotheses advanced to explain the causes of the clinical manifestations and death in upper intestinal obstruction are (1) reflex nerve disturbance causing cardiac or vasomotor paralysis, (2) infection of the peritoneum and blood stream from increased permeability of the intestinal walls for bacteria, (3) failure for the opportunity for neutralization of toxins of the upper intestinal tract by substances in lower segments, and (4) the development of toxic substances in the proximal portion of the intestine and their systemic absorption. The last hypothesis seems worthy of much consideration.

In 1909, Draper<sup>1</sup> defined an "oral, lethal line" in the duodenum between the ampulla and pylorus. He says that ligation of the pylorus causes "physiological death" less often than lower occlusions. Whipple, Stone and Bernheim,<sup>2</sup> in 1914, using closed duodenal loops in dogs, showed rather conclusively that a toxic substance is formed, which when injected into animals produces a picture identical with that obtaining in the obstructed animal. As possible agents, they eliminated bile, gastric and pancreatic juice and certain toxic substances such as split-food products. They claim that the toxic substance is either formed in the duodenal mucosa or is a product of bacterial autolysis, or both. The removal of the duodenal mucosa prevents the formation of this toxic substance. Hartwell, Hoguet and Beekman,<sup>3</sup> in 1914, working along similar lines, came to somewhat different conclusions and maintained that it is lack of water absorption or excessive loss of fluid, in conjunction with elaboration of a cellular poison from a gangrenous duodenal mucosa which accounts for the toxemia and death in high intestinal obstruction. They emphasized the changes in the duodenal mucosa as of great importance. Dragstedt<sup>4</sup> and others believe

1 Draper, J. W. Intestinal Obstruction. An Outline for Treatment Based upon the Cause of Death, *Am J M Sc* **137** 725-739, 1909.

2 Whipple, G. H., Stone, H. B., and Bernheim, B. M. Intestinal Obstruction. III. The Defensive Mechanism of the Immunized Animal Against Duodenal Loop Poison, *J Exper M* **19** 144-165, 1914.

3 Hartwell, J. A., Hoguet, J. P., and Beekman, F. An Experimental Study of Intestinal Obstruction, *Arch. Int Med* **13** 701-736 (May) 1914.

4 Dragstedt, L. R., and Dragstedt, C. A. Acute Dilatation of the Stomach, *J A M A* **79** 612-615, 1922.

and demonstrated similar increases after proteose injections. Histologically they were unable to find renal lesions. Subsequently, McQuarrie and Whipple,<sup>19</sup> in an experimental study of intestinal obstruction and proteose intoxication, proved conclusively that renal function was definitely impaired. They found a decreased elimination of phenolsulphonephthalein and chlorids in the urine with increased concentration of urea in the blood, and pointed out the possible clinical importance of these observations.

Hardt and Rivers<sup>20</sup> have reported an interesting and important group of cases in which, during the course of alkaline treatment for ulcer, toxic symptoms developed. Their cases exhibited albuminuria, cylindruria and a rise in the blood urea and in the alkaline reserve, there was also clinical evidence of renal insufficiency. In the two cases coming to necropsy, an acute exacerbation of chronic nephritis was found.

Tisdall's<sup>21</sup> observations indicate that the sodium-calcium relation is not disturbed in gastric tetany. These findings we are able to substantiate.

Credit for recognizing the clinical importance of the renal factor in the toxemia and death following gastro-enterostomy belongs to Tucker,<sup>22</sup> formerly of the Mayo Clinic, who reports eight cases from the Clinic in which uremia developed following gastro-enterostomy. He believed uremia to be the probable cause of death. In four of his cases, necropsy revealed the grafting of an acute process on a previously existing chronic nephritis. It is significant that in not a single instance did he find any local, organic lesion in the wall of the intestine adequate to explain the toxemia and death. From an experimental and clinical point of view, the following conclusions seem to be established:

- 1 Complete continued obstruction of the duodenum or upper jejunum causes a fatal toxemia.

- 2 The obstructed duodenal contents, when injected into animals, cause symptoms of intoxication similar to those obtaining in the obstructed animal.

- 3 Blood analysis shows (a) decreased plasma chlorids, (b) increased carbon dioxide combining power of the plasma, and (c) increased blood urea.

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19 McQuarrie, I, and Whipple, G. H. I. Renal Function Influenced by Intestinal Obstruction, *J. Exper. M.* **29** 397-419, 1919. II. Renal Function Influenced by Proteose Intoxication, *J. Exper. M.* **29** 421-444, 1919.

20 Hardt, L. L., and Rivers, A. B. Toxic Manifestations Following the Alkaline Treatment of Peptic Ulcer, *Arch. Int. Med.* **31** 171-180, 1923.

21 Tisdall, F. F. The Influence of the Sodium Ion in the Production of Tetany, *J. Biol. Chem.* **54** 35-41, 1922.

22 Tucker, W. J. Uremia Following Gastro-Enterostomy, Eight Cases, *Wisconsin M. J.* **20** 528-529, 1922.

the plasma and an increase of the alkaline reserve. They obtained similar nerve reactions following the intravenous administration of large quantities of carbonate or bicarbonate of soda, which indicates the importance of the disturbance of the acid-base equilibrium.

Hastings, Murray and Murray<sup>11</sup> confirmed the changes in carbon-dioxid combining power and chlorids of plasma in experimental pyloric closure. No significant changes were noted in the hydrogen-ion concentration of the serum, but sulphur and phosphorus were markedly increased.<sup>12</sup> Harrop<sup>13</sup> and Healy<sup>14</sup> described tetany in accidental sodium bicarbonate poisoning in cases without gastric lesions. Tileston and Comfort<sup>15</sup> have shown a marked increase of total nonprotein nitrogen and urea in the blood in cases of acute intestinal obstruction. They were not inclined to ascribe this to renal injury, but rather to increased tissue destruction, for two reasons, first, the retention of nitrogen disappeared following operative relief of the obstruction, second, the retention was associated with indicanuria. They admit that decreased elimination of nitrogen and loss of fluid may play a part.

Louria<sup>16</sup> and Rabinowitch<sup>17</sup> have reported similar increases in the nonprotein nitrogen of the blood in postoperative ileus, general peritonitis and acute pancreatitis. An analysis of these cases indicates that they differ from those included in our group. They are not of the tetany type, but include many varied pictures of the intra-abdominal infections. Necropsy studies in the cases of Louria and Rabinowitch did not reveal renal lesions, at least not the renal lesions appearing in our cases.

Cooke, Rodenbaugh and Whipple<sup>18</sup> verified in animal experiments the existence of an increased nonprotein nitrogen content in the blood,

11 Hastings, A. B., Murray, C. D., and Murray, H. A., Jr. Certain Chemical Changes in the Blood After Pyloric Obstruction in Dogs, *J Biol Chem* **46** 223-232, 1921.

12 Greenwald holds that in parathyroprival tetany phosphoric acid is retained and that the condition is not one of alkalosis but of acidosis. Greenwald, I., and Lewman, Gertrude. The Determination of the Titratable Alkali of the Blood, *Jour Biol Chem* **54** 263-283, 1922.

13 Harrop, G. A., Jr. The Production of Tetany by Intravenous Infusion of Sodium Bicarbonate, *Bull Johns Hopkins Hosp* **30** 62-63, 1919.

14 Healy, W. P. Postoperative Tetany Due to Sodium Bicarbonate, *Am J Obst & Gynec* **2** 164-170, 1921.

15 Tileston, W., and Comfort, C. W., Jr. The Total Nonprotein Nitrogen and the Urea of the Blood in Health and in Disease, as Estimated by Folin's Method, *Arch Int Med* **14** 620-649 (Nov) 1914.

16 Louria, H. W. The Blood Urea Nitrogen in Acute Intestinal Obstruction, *Arch Int Med* **27** 620-628, 1921.

17 Rabinowitch, I. M. The Prognostic Value of the Study of the Blood Chemistry in the Acute Abdomen, *Canad M A J* **11** 163-166, 1921.

18 Cooke, J. V., Rodenbaugh, F. H., and Whipple, G. H. Intestinal Obstruction. VI. A Study of Non-Coagulable Nitrogen of the Blood, *J Exper M* **23** 717-738, 1916.

patient had vomited at least once in twenty-four hours, and food retention of twelve hours had been noted. The weight loss of 25 pounds (11.33 kg) had been progressive. Blood had not been noted in the vomitus or stools.

On examination, the patient appeared to be extremely sick, he was emaciated, weak, and had a dry skin. There was slight diffuse tenderness in the epigastrium. In the right hypochondrium an indefinite, sausage-shaped mass was palpable, movable and slightly tender. The edge of the liver was felt. The ophthalmoscopic examination was negative. The systolic blood pressure was 98, the diastolic, 80. Two months before, the readings had been 125 systolic and 75 diastolic. The gastric contents revealed total acidity, 26, free hydrochloric acid, 14, food remnants, 1 and sarcines, 1, the total amount of contents recovered being 700 cc. Roentgenologic examination revealed retention 2 (on the basis of 1 to 4), but no lesion. With the exception of an occasional hyaline cast, no abnormalities were found in the urine. The blood contained hemoglobin, 76 per cent (Dare), erythrocytes, 4,720,000, and leukocytes, 7,200. The blood urea was 124 mg, and creatinin 23 mg for each 100 cc. The phenolsulphonephthalein (intravenously) excretion was 10 per cent.

A diagnosis was made of pyloric obstruction with chronic nephritis and marked renal insufficiency. In view of the serious condition of the patient, operation was not deemed advisable at the time and medical management was instituted, consisting of glucose and alkalis by rectum, limited liquids by mouth and gastric lavage twice daily. Alkalis were stopped when alkalosis was recognized. On September 24, after a motor meal, no retention was demonstrated. The condition of the patient remained constant until September 30, when he had a slight convulsion, characterized by generalized quivering. His pulse was feeble and he seemed much weaker. One-half hour later the patient vomited 600 cc of a thin, pea-soup fluid. He complained of tingling sensations in the face and hands, later in the day, the vomiting became almost continuous. His mental condition remained clear until October 2, when definite mental aberration was noted. An exploratory operation was performed and a gastro-enterostomy in an attempt to relieve the obstruction. A hard, firm mass was found 15 cm below the pylorus involving the duodenum and the head of the pancreas. The proximal portion of the duodenum was dilated as was the stomach. Immediately following the operation the patient exhibited muscular twitchings, five cubic centimeters of 5 per cent calcium chlorid solution were administered intravenously every six hours. On the second day his condition remained about the same, but toward evening he became unconscious and died the next day.

At necropsy the pancreas was found to be normal in size, and its duct was patent throughout. In the outer portion of the head, near the central portion of the duodenum, was a firm mass. The first portion of the duodenum was greatly distended. On opening it a hard, round, crater-like ulceration with thickened, indurated margins was found 1 cm below the pylorus and 3 cm above the ampulla of Vater. This mass was intimately adherent to the pancreas and continuous with the small pancreatic mass previously mentioned. The duodenal wall in this region was thickened and very firm in consistency. An opening was found in the greater curvature of the stomach 5 cm proximal to the pylorus, which admitted three fingers and opened into the jejunum 5 cm from the duodenojejunal juncture. There was no leakage at the suture line. The right and left kidneys weighed, respectively, 180 and 215 gm. The capsules stripped with ease and left a smooth, congested surface. On section, the organs were moderately congested throughout, and the markings of the cortex and column of Bertini were indistinct. The rays of the pyramids appeared as red lines and were fairly prominent. Scattered over the cortex of both kidneys were numerous, pin-point, whitish nodules. In the mucosa of the pelvis of the left kidney were a few tiny foci of hemorrhages. There were no abnormalities noted in the remainder of the genito-urinary tract. The heart weighed 350 gm. The myocardium was soft and flabby and had a slight brownish tinge. In the



4 There is no unanimity of opinion as to the nature of the toxic substances or as to the exact cause of death, but Whipple's and Dragstedt's work ascribing the toxemia to the formation of substances of a proteose nature produced in the duodenum is the most convincing evidence available, while Gerard's suggestion that histamin is responsible for the toxemia is worthy of consideration

*A Clinical Study of Duodenal Intoxication*—This report is concerned with the clinical, pathologic and biochemical studies in a series of eleven cases of duodenal toxemia, the patients are classified in two groups

Group 1 The preoperative group, in which the obstruction followed an organic lesion involving the duodenum, five cases Case 1, carcinoma of the middle portion of the duodenum, Case 2, duodenal ulcer with pyloric obstruction, Case 3, carcinoma of the stomach, involving the pylorus with obstruction, Case 4, chronic duodenal ulcer with stenosis, and Case 5, carcinoma of the pancreas, obstructing the lower third of the duodenum

Group 2 The postoperative group, in which organic duodenal obstruction or functional stasis followed operation, six cases, considered in two groups (a) acute duodenal obstruction in which symptoms appeared from five to eleven days following operation, Case 6, posterior gastro-enterostomy for duodenal ulcer followed in five days by obstructive toxemia No anatomic explanation was found in the duodenum to account for the toxemia, Case 7, posterior gastro-enterostomy for saddle ulcer of the first and second portions of the duodenum (involving the pancreas), clinical evidences of obstruction appearing ten days later, Case 8, posterior gastro-enterostomy for duodenal ulcer 125 cm below the pylorus Mild obstructive symptoms were noted five days later (b) Chronic duodenal obstruction in which symptoms appeared from six weeks to six months or more after operation on the stomach or duodenum Case 9, gastrojejunal ulcer six years after a posterior gastro-enterostomy, Case 10, gastro-enterostomy for duodenal ulcer, there were chronic obstructive symptoms for five years, there was kinking of the jejunoduodenal juncture, Case 11, gastro-enterostomy for supposed duodenal ulcer, obstructive symptoms appeared six months later, there were adhesions and kinking of the proximal loop

#### REPORT OF CASES

In the following case reports the degree of retention obstruction, casts etc., is represented by a figure on the basis of grades 1 to 4

CASE 1 (A333574)—Mr W R T, aged 61, entered the Mayo Clinic on Sept 11, 1920, complaining of epigastric distress of six months' duration having begun as a dull, aching pain The periods of remission from pain had not exceeded three days The pain was exaggerated two or three hours after eating and was not relieved by food or alkalis For the last two months the

TABLE 1—Findings in Case 1

Date	Blood				Urine			Blood Pressure		Remarks
	Hemo- globin (Dare) Per- centage	Urea, Mg for Each 100 C c	Creatinin, Mg for Each 100 C c	Carbon Dioxid, Volume, Per- centage	Albu- min	Sediment	Phenol- sulphone phthalein, Percentage	Sys- tole	Dias- tole	
7/10/20	76					Hyaline casts 1		125	75	Before admission
9/13/20	78					Hyaline casts 1	10	98	80	Continual vomiting
9/16/20		124	2.3		1	Hyaline casts 1				Continual vomiting
9/21/20		120	1.7		2	Hyaline casts 1	No return	98	80	Continual vomiting
9/23/20					2		5			Continual vomiting
9/28/20	82	100			2	Hyaline casts 1		98	80	Nervous manifestations of tetany
9/30/20										Chvostek positive
10/ 2/20				158						

TABLE 2—Chemical Studies of the Blood During Period of Duodenal Tormenta (Case 2)

Date	Urine				Blood				Phenol- sulphone- phthalein Excre- tion, Per- centage	Hemo- globin (Dare)	Erythro- cytes 4,500,000	Leuko- cytes 7,400	Gastric Acids		Blood Pressure		Blood	
	Specific Gravity	Reac- tion	Albu- min	Eryth- rocytes	Carbon Dioxid, Volume, Per- centage	Urea, Mg for Each 100 C c	Plasma Chlor- ids, Mg	Free Hydro chloric					Total	Sys- tole	Dias- tole	Sodium, Mg for Each 100 C c	Potas- sium, Mg for Each 100 C c	
9/26/21	1 014	Acid	1	2	80	4.3	225											
9/29/21	1 011	Alkaline	1		82	4.7	161											
10/ 1/21	1 013	Alkaline			82		170											
10/ 4/21					86	5.5	214											
10/ 6/21					78	4.5	226											
10/ 8/21	1 009	Acid	1	1	76	4.4	226											
10/10/21	1 012	Acid	1	1	58	4.4	198											
10/12/21	1 013	Acid	1	1	62	3.8	100											
10/14/21	1 011	Acid	1	1	59	3.5	196											
10/17/21	1 011	Acid	1	1	59	3.5	105											
10/19/21					59	2.9	73											
10/21/21					56	2.6	623											
10/24/21						2.2	43											
10/27/21	1 011	Acid	1			2.3	39											
11/ 2/21					56		670											
11/ 8/21	1 010	Acid	1				635											
11/11/21	Gastro enterostomy						640											
11/23/21	1 015	Acid	1		50	2.1	30											
11/28/21					71	2.7	635											
						2.4	35											

coronary arteries, more especially in the left root of the aorta and the leaflet of the mitral valve, were numerous small patches of yellowish thickening. The lungs revealed small areas of bronchopneumonia.

The histologic examination of the heart muscle revealed areas of marked fragmentation. Sections of the lungs showed small areas of bronchopneumonia. The glomeruli of the kidney were lobulated and decreased in size. Small areas of lymphocytic infiltration were seen in the interstitial tissue. The tubules revealed degeneration in certain areas. There was slight increase in the interstitial tissue throughout the section (Fig 1). The muscular and submucosal layer of the duodenum revealed infiltration by cells having a definite glandular arrangement. The cells were epithelial-like and were divided into small islands by bands of fibrous tissue.

The case was one of primary carcinoma of the duodenum causing obstruction and chronic distention of the first portion of the duodenum and stomach. There was marked evidence of renal insufficiency as

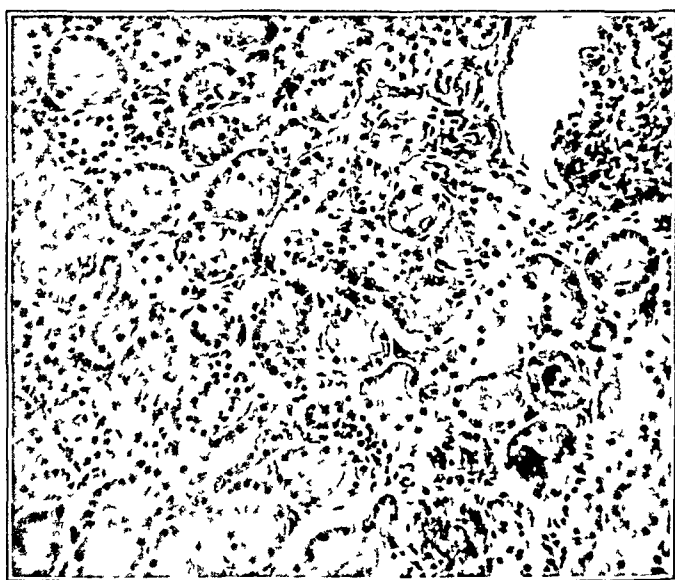


Fig 1 (Case 1)—Section of kidney showing areas of tubular degeneration and calcareous deposits in the tubules ( $\times 100$ )

shown by the urine and in the increase of blood urea and creatinin and the low excretion of phenolsulphonephthalein. The clinical picture was that of gastric tetany and uremia associated with a high grade alkalosis. Muscular twitchings, vomiting, mental aberration and asthenia with associated blood findings constitute a syndrome that cannot be differentiated from that of uremia. The necropsy findings of severe toxic nephritis bear out this assumption (Table 1).

CASE 2 (A297046)—Mr F W M, aged 52, came to the Clinic on Sept 25, 1921, complaining of gastric distress of fifteen years' duration with remissions for periods as long as three years. The distress came on about two and one-half hours after meals, and was especially marked during the night. Relief was usually obtained by food and alkalis. Three years earlier the condition was diagnosed duodenal ulcer, and medical treatment was given. Albumin was

by nausea. For the last three months the condition had been much worse. Only liquid foods had been eaten, but nausea and vomiting had occurred frequently.

Gastric analysis revealed total acidity 34 with free hydrochloric acid 16, a total of 1,024 cc of gastric contents were recovered. Roentgenograms of the stomach revealed dilatation 3, with a lesion at the outlet. The systolic blood pressure was 130, and the diastolic 98. The specific gravity of the urine was 1.026, albumin 1, and the sediment was negative. The blood contained hemoglobin, 68 per cent (Dare), erythrocytes 4,270,000 and leukocytes 4,600.

The patient was sent to the hospital for preoperative treatment. With daily gastric lavage, amounts were recovered varying from 500 to 1,500 cc of thin, greenish fluid. Liquids were forced and glucose given by rectum, the patient was kept on a liquid diet. Two attacks of tetany occurred while the patient was under medical care, the second consisting of a tetanic type of convulsion, lasting thirty minutes and followed by marked prostration. The patient's general condition was not good. The fourth day after his admission to the hospital the blood urea was 80 mg, the carbon dioxide 105 volumes per cent. On August 13, five days after admission, a posterior gastro-enterostomy was performed. A tumor of the pylorus, which seemed to be causing almost complete obstruction, was found. It was impossible to determine whether or not the tumor was malignant, but it seemed to be a polyp. The operation was regarded as an emergency procedure because of the gastric tetany and renal insufficiency. Following the operation the patient became excitable and mildly delirious. His respiration was increased to 36. Fluids were given subcutaneously and by proctoclysis. Nothing important was discovered on physical examination. The same evening gastric lavage produced 240 cc of dark fluid, after which the patient felt fairly well. August 17, the specific gravity of the urine was 1.021, it contained albumin 2, hyaline casts 1. The blood urea was 88 mg for each 100 cc, the blood creatinin, 24 mg. Convalescence was uneventful. A second operation was performed on September 5, when a carcinoma of the posterior wall of the stomach just above the pylorus was removed with about one-third of the stomach. This growth had a crater, but was not adherent posteriorly to the pancreas. The pathologists reported carcinoma without glandular involvement. The patient was dismissed from observation eighteen days after operation, at which time the values for blood nitrogen were normal, but a constant trace of albumin was still found in the urine.

This patient presented a long-standing history of epigastric distress of an obstructive nature, which was not typical of duodenal ulcer. For the last three months, retention features had been present, which were verified by clinical and laboratory examinations. While under medical management gastric tetany with renal insufficiency became evident. Diagnosis of toxic nephritis was made and surgical relief was given by removal of neoplasm of the duodenum before the condition had progressed to the fatal stage.

CASE 4 (A317395)—Mr O P, aged 27, came to the Clinic on May 27, 1920, complaining of having had pain in the stomach, attacks of abdominal pain, nausea, vomiting, dizziness, constipation and occasional severe attacks of jaundice for eight years. Tarry stools and hematemesis had also been noted. The attacks recurred every five to eight months. The pain reached its maximum three hours after eating and after midnight. It was not relieved by food or soda, but usually by vomiting. The patient had lost 20 pounds (9.07 kg) in weight, was easily exhausted and had syncopal attacks. He had not had special nervous symptoms, with the exception of insomnia.

found in the urine, but there was no other evidence of renal insufficiency. For one year there was freedom from gastric symptoms. The present attack had begun ten days before admission. Relief from pain had been obtained by an exclusive milk diet and large doses of alkalis. Three days later he had begun to vomit and this continued. The patient said that everything he ate "seemed to back up" on him.

In the course of the routine laboratory examination, a blood urea of 222 mg for each 100 c.c. was found. The systolic blood pressure was 124 and the diastolic 98. A trace of albumin, hyaline and granular casts and occasional erythrocytes were found in the urine. Mild but distinct mental symptoms existed as evidenced by irritability and slight drowsiness. Because of the renal insufficiency, the patient was hospitalized for medical treatment preparatory to operation for duodenal ulcer. The treatment consisted of 1 liter of 5 per cent glucose solution by rectum, 1 liter of milk by mouth and high carbohydrate and low protein diet. Dilute hydrochloric acid and calcium chloride were given by mouth. No obstruction was demonstrable by barium or twelve-hour motor meals. Under this regimen, the patient improved rapidly (Table 2). No alkalis were administered. Following the improvement in the renal condition, the patient was allowed to return home for ten days before the anticipated operation.

The operation was performed on November 11, by W. J. Mayo. An ulcer covering three-fourths of the circumference of the duodenum was found extending up to and involving the pylorus. Obstruction 3 (on the basis of 1 to 4) was found. The tip of the finger could not be introduced into the pyloric canal. The appendix was removed. The gallbladder was adherent, but was not removed. The patient's convalescence was uneventful and renal functional studies showed a marked improvement. An examination was made eight months later, and slight impairment of renal function was still found. The phenolsulphonephthalein excretion in two hours was 40 per cent and the blood urea 46 mg for each 100 c.c. The systolic blood pressure was 155 and the diastolic 90. The urine contained albumin 2 and hyaline and granular casts 1. The patient's general physical condition was excellent.

A man, aged 52 years, with a long-standing history of duodenal ulcer, during an active stage of the ulcer, developed evidences of uremia. This was shown both in clinical and laboratory examinations. A definite alkalosis was present which may stand in causal relationship to excessive use of alkalis. The plasma chlorids were moderately reduced. No evidence of tetany was present. The important part played by the kidney in the clinical picture is demonstrated by markedly low excretion of phenolsulphonephthalein with a high urea and creatinin level in the blood, and evidence of renal irritation in the urine. The absence of elevated blood pressure allows us to classify this renal injury as a nephrosis. Operation resulted in a clinical cure with the disappearance of all symptoms and marked improvement in renal function.

CASE 3 (A367847).—Mr. H. L., aged 54, came to the Clinic on Aug. 9, 1921, because of stomach trouble of twenty years' duration, characterized by considerable nervous indigestion, with occasional vomiting of food at night. Five years before, the patient had had a gastric hemorrhage and melena. Following medical treatment he was in good health for two years. For the last two years he had been constipated, his abdomen was bloated and he frequently vomited food eaten the day before. Vomiting was always preceded

TABLE 3—Findings in Case 5

Date	Blood					Urine				Remarks		
	Hemoglobin, Acid- Hematin, Per centage	Urea, Mg Each 100 C c	Carbon Dioxide, Per Volume, centage	Chlorids, Mg for Each 100 C c	Sodium of Serum, Mg for Each 100 C c	Albu- min	Sediment	Total Nitro- gen, Gm	Phenol- sulphone- phthalen, Percentage Intravenously		Blood Pressure	
											Sys- tolic	Dias- tolic
12/26/22	85	88	101	375		2	Hyaline, granular		30	109	78	Gastric acids, total 40, free 0
12/27/22										118	78	
12/29/22	90	62	150	425		1	Hyaline and granular casts	10.7				
12/31/22	90		112	456	348 337	1						
1/ 2/23		38	163	395						120	80	Hydrogen ion concentration of blood plasma, $p_{\text{H}}$ 7.4, urine chlorids, 0.34 gm Gastric acids, total 34, free 16 Hydrogen ion concentration of blood plasma, $p_{\text{H}}$ 7.2, of urine, $p_{\text{H}}$ 7.2 Sodium in urine, 278 mg for each 100 C c
1/ 3/23		54	144	425								
1/ 4/23			133	450		3	Hyaline and granular casts				50	
1/10/23	80		126	600								
1/12/23			114	670								

Examination was practically negative except for distant heart sounds and definitely infected tonsils. The systolic blood pressure was 100 and the diastolic, 90. The urine was negative. The blood contained hemoglobin, 68 per cent (Dare), erythrocytes, 4,050,000, leukocytes, 6,200. The gastric analysis revealed total acidity 80 and free hydrochloric acid 60, the total of gastric content recovered was 3615 c.c. Roentgenograms of the stomach revealed a perforating duodenal ulcer, with retention 3. The clinical diagnosis was chronic perforating duodenal ulcer with history of obstruction.

The patient's condition was considered grave, and he was referred to the hospital for preoperative medical treatment. Daily gastric lavage, fluids by rectum, liquid diet, and proctoclysis of sodium chlorid solution were given. Each lavage was followed by immediate relief, the amounts recovered averaged 300 to 1,000 c.c., and the fluid was of a thin, serous type. On the third day, the patient complained of numbness of the fingers and difficulty in speaking. The systolic blood pressure was 110 and the diastolic 80. Neurologic examination revealed positive Chvostek and Trousseau signs. A diagnosis of gastric tetany was made. Aphonia followed the passing of the stomach tube. Calcium chlorid was given intravenously.

Operation was performed on June 8. The first part of the duodenum was found to be definitely contracted. The stomach was dilated, 4. A posterior gastro-enterostomy was performed. The patient became delirious and required morphin. However, he soon improved, and his temperature and pulse were normal for several days. Sodium chlorid by proctoclysis was given, with small amounts of water by mouth. One thousand and fifty cubic centimeters of urine were passed during the second twenty-four hours. The patient vomited occasionally, was very restless and at times irrational. His condition remained fairly satisfactory until the seventh day after the operation, then pain developed in the abdomen and the temperature and pulse rate increased, with other evidences of peritonitis. He died the ninth day after the operation.

Necropsy revealed general serofibrinous purulent peritonitis, an old healed duodenal ulcer with stenosis of the pylorus, double empyema with terminal bronchopneumonia, acute diffuse nephritis and acute hypoplasia of the lymphoid tissues of the body.

Histologic examination of the kidneys revealed increased interstitial connective tissue, lymphocytic infiltration in the stroma of the cortex and medulla and numerous foci of calcium salts with mulberry-like form. The crystals filled more particularly the collecting tubules.

This patient, with a typical history and clinical findings of duodenal ulcer with obstruction, following the institution of medical treatment, developed symptoms of duodenal intoxication with gastric tetany. At operation stenosis of the duodenum was found, and gastro-enterostomy was performed for relief. Death from general peritonitis and double empyema occurred in seven days. Necropsy revealed acute diffuse nephritis. This case was one of the earliest in the series, and blood chemistry and renal function studies were not made.

CASE 5 (A413425)—Mr. J. C. C., aged 38, came to the Clinic on Dec. 25, 1922, because of gastric trouble of nine months' duration. He had been jaundiced about seven months before, but did not have pain. A cholecystostomy had been performed, and the symptoms were relieved. In October, a second operation had been performed to close the biliary fistula and to explore the stomach because of obstructive symptoms. A large mass was found involving the pancreas, which was diagnosed malignant. In order to relieve the common-duct obstruction, a tube was placed with one end in the gallbladder, the other end in the jejunum and united extra-abdominally, and a gastro-

a total acidity of 36 and a free acidity of 17. In thirty-six hours, the patient became drowsy and shortly afterward had a convulsion which was characterized by clenching of the hands, twitching of the facial muscles and clonic contractions of the whole musculature. This was followed by coma. The pulse was very weak, respirations were shallow, but the color remained good. Three more attacks occurred during the next twenty-four hours (Fig 2). One thousand cubic centimeters of sodium chlorid solution were given subcutaneously and 500 cc of glucose solution by rectum, this did not control the convulsion. Eight hundred cubic centimeters of Ringer's solution containing an additional gram of calcium chlorid were given intravenously followed by a solution of sodium chlorid and glucose by rectum. In eight hours there was definite improvement, the patient was more rational and he had no more convulsions,

TABLE 4—*Nitrogen Partition of Blood in Case 5\**

Date		Mg for Each 100 Cc	Percentage of Nonprotein Nitrogen
12/27/22	Total nonprotein nitrogen	75.0	100.0
	Urea nitrogen	49.0	65.0
	Creatinin nitrogen	0.89	1.6
	Uric acid nitrogen	2.46	3.3
	Amino nitrogen	7.20	9.6
	Rest nitrogen	15.25	20.5

Nitrogen Partition of Urine			
		Gm	Percentage
12/27/22	Total nitrogen	16.0	100.0
	Urea nitrogen	12.50	78.0
	Creatinin nitrogen	0.50	3.1
	Uric acid nitrogen	0.33	2.0
	Ammonia nitrogen	0.585	3.6
	Amino nitrogen	0.165	1.0
	Rest nitrogen	2.0	12.5

\* The nitrogen partitions in this case were made by Dr. C. H. Green.

TABLE 5—*Hydremia and Blood Volume Studies (Case 5)*

Date	12/31/22	1/10/23
Water content of whole blood, percentage	82.5	83.2
Water plasma, percentage	91.3	91.2
Hematocrit values—Erythrocytes, percentage	30.0	34.0
Plasma, percentage	70.0	66.0
Total plasma volume, cc	2062	2857
Plasma, cc for each kilogram	54	57
Total blood volume, cc	4231	4328
Blood, cc for each kilogram	78	86
Haldane Palmer hemoglobin, percentage	90.0	80.0

although he was restless and talked irrationally at times. He continued to improve, and 20 gm of sodium chlorid and 600 cc of water were passed daily through the tube into the duodenum, with feedings of lactose, glucose and peptonized milk. His condition continued to improve. There was a decrease of blood urea and increasing phenolsulphonephthalein excretion. Obstructive symptoms were constant and larger amounts were recovered than given. On January 12, an exploratory operation was performed. General carcinomatosis was found, which involved the liver, pancreas and peritoneum. In the stomach and jejunum was a large mass of carcinomatous tissue. The patient died from exhaustion the third day after operation (Tables 3, 4 and 5).

Necropsy revealed carcinoma of the pancreas with peritoneal carcinomatosis and metastasis to the liver, obstruction of papilla of Vater and duodenal lumen with dilatation of the common duct, ancient gastro-enterostomy, recent enterostomy, ancient cholecystostomy, hypostatic edema and congestion of the lungs.



enterostomy was performed. The patient did very well following the operation up to two weeks before coming to the Clinic, when he began to develop definite symptoms of pyloric obstruction.

Examination revealed emaciation and evidence of dehydration. There was no jaundice. A rubber tube about 15 cm. in length lay across the abdomen, one end apparently passing into the gallbladder and the other into the duodenum, bile was passing through the tube freely. A large mass could be

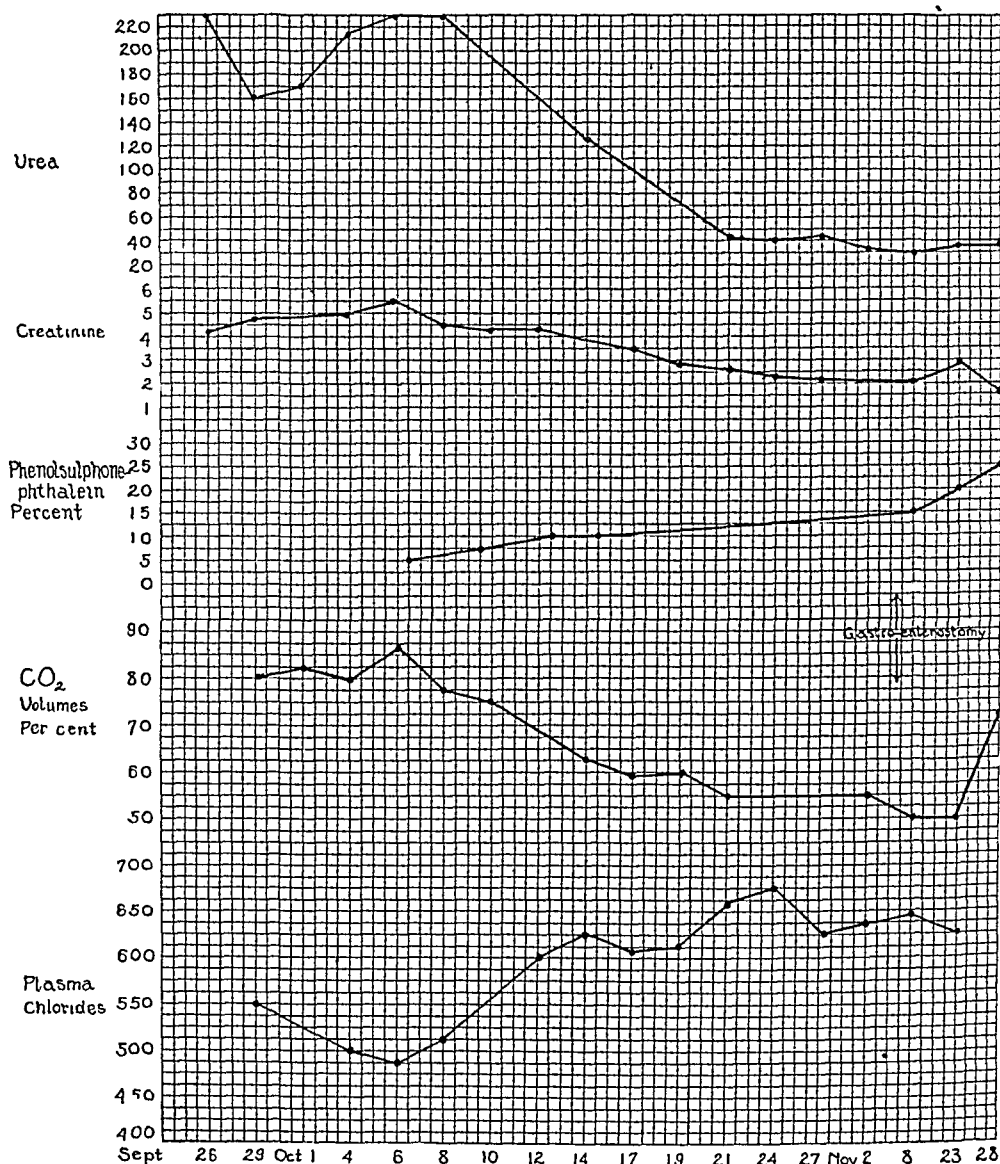


Fig 2 (Case 5)—Chart showing blood chemistry and renal function in duodenal toxemia

palpated in the upper right quadrant which was apparently the liver or pancreas. The superficial abdominal veins were prominent. The urine was acid, it contained albumin 2 and a few pus cells. There were 15,000 leukocytes, 4,720,000 erythrocytes and 90 per cent hemoglobin (Haldane-Palmer). The carbon-dioxid combining power of the blood was 101.

The patient was hospitalized for treatment on December 26. The first twenty-four hours he vomited about 800 c.c. of a watery, faint yellow fluid, with

On February 28, the patient vomited 350 c c of greenish fluid and later with gastric lavage 800 c c of fluid were recovered, after which the patient made fair progress for four days. On March 3, the patient complained of epigastric distress and lavage recovered a large amount of thin, greenish fluid. The patient seemed definitely weaker, somewhat dull mentally, and the pulse and respiration were slow. Trousseau and Chvostek reactions were not obtained.

TABLE 6—*Findings in Case 6*

Blood Chemistry					
3/2/22	Urea, mg for each 100 c c				192
	Carbon dioxide, volumes percentage				84
	Plasma chlorids, mg for each 100 c c				320
	Creatinin, mg for each 100 c c				3.7
	Total nonprotein nitrogen, mg				147
	Sodium, mg for each 100 c c				412
	Potassium, mg for each 100 c c				20.6
Hydremia Studies					
	Whole blood viscosity				7.2
	Specific gravity, whole blood				1.070
	Palmer Haldane hemoglobin, percentage				116
	Water content of whole blood, percentage				78.3
	Specific gravity of the plasma				1.035
	Water plasma, percentage				92.8
	Hematocrit values—Erythrocytes, percentage				46.2
	Plasma, percentage				53.8
	Total nitrogen, mg				0.909
Nitrogen Content in Gastric Secretion, Mg for Each 100 C c					
	Reaction	Ammonia Nitrogen	Combined Urea and Ammonia Nitrogen	Urea Nitrogen	Estimated* Urea
3/2/22	Markedly alkaline	90	90	0	192.6

\* Obtained by assuming the free ammonia to be derived in toto from urea. Therefore the combined urea and ammonia nitrogen is the correct index for estimating the urea, not the urea nitrogen alone.

TABLE 7—*Chemical Data of Postmortem Fluids and Tissues (Case 6)*

Fluids					
	Blood urea, mg for each 100 c c				143*
	Blood plasma chlorids, mg for each 100 c c				253
	Spinal fluid urea mg for each 100 c c				296
Tissue, Mg for Each 100 C c					
	Ammonia Nitrogen	Combined Urea and Ammonia Nitrogen	Urea Nitrogen	Estimated Urea	
Kidney	29.8	134.5	104.6	387.0	
Stomach	75.0	263.9	194.0	575.0	
Liver	24.3	188.0	163.7	402.3	
Estimation of Chlorids					
	Wet Weight, Gm	Dry Weight, Gm	Water, Gm	Sodium Chlorid, Mg for Each 100 Gm Fresh Tissue	
Kidney	5	0.775	4.225	400	
Stomach	5	0.850	4.150	200	
Liver	5	1.352	3.648	400	

\* Probably low

At times the hands assumed the position characteristic of tetany. The systolic blood pressure was 80 and the diastolic 55. The extremities were cold, and there was some cyanosis of the hands, with a florid red color of the cheeks and ears. The skin was dry, and the features were sunken. The temperature and pulse were normal. At 11 a. m., the patient developed symptoms of tetany, slight tonic convulsions, typical position of the hands and partial unconsciousness. He died in complete coma the following morning (Tables 6 and 7).

and acute diffuse nephritis. The left kidney weighed 180 gm and the right 205 gm, the right was extremely congested and edematous, the cortex was thickened, the markings were indistinct, the left kidney did not present gross abnormalities.

This patient<sup>23</sup> had carcinoma of the pancreas obstructing the lower third of the duodenum. Obstructive symptoms were present for three months. The first examination revealed the usual chemical and clinical evidence of duodenal toxemia with gastric tetany. Renal insufficiency was demonstrated by albuminuria, azotemia and diminished phenolsulphonephthalein excretion. The total nitrogen excretion in the urine revealed a normal amount for the twenty-four hours. The excretion of this quantity of nitrogen on a low protein diet and in the presence of a definite renal injury would seem to indicate an abnormally high degree of protein destruction. No leucin or tyrosin crystals were found. No evidence of sodium poisoning was obtained as normal values were found in the blood. No significant change was noted in the hydrogen-ion concentration of the blood. The shock features were not pronounced. The total blood and plasma volumes were within normal limits. Following treatment the total blood volume was not definitely increased. It is interesting to note the improvement in renal function, following the control of the toxemia by treatment. Necropsy revealed malignant obstruction of the duodenum and acute diffuse nephritis.

CASE 6 (A383808)—Mr A F H, aged 32, came to the Clinic on Feb 10, 1922, because of epigastric distress of twelve years' duration. An appendectomy had been performed one year before, without relief. The patient had had periods of distress once or twice yearly, which continued for from two to four months. The pain usually reached its height about two hours after eating. Relief was obtained by food and soda, and partial relief by a diet of milk and cereal. Occasionally he vomited food eaten twelve hours before.

The patient was well developed, of good color, and weighed 150 pounds (68 kg). The systolic blood pressure was 120 and the diastolic 70. The blood contained hemoglobin (Dare), 79 per cent, erythrocytes, 4,800,000, and leukocytes, 4,460. Urinalysis was negative. Gastric analysis showed a total acidity of 70 and free hydrochloric acid of 50, a total of 170 cc of gastric content was recovered. The blood urea amounted to 33 mg for each 100 cc. The roentgenologist reported "duodenal ulcer without obstruction." The diagnosis of duodenal ulcer was clear cut, and surgical treatment was advised.

Operation was performed on February 20. An ulcer with a large amount of induration, due to inflammatory reaction, was found below the pylorus. There was obstruction, and the stomach was dilated 2. A posterior gastro-enterostomy was performed. The convalescence was uneventful until the fifth day, when the patient complained of a sensation of fulness in the abdomen with distress and discomfort. Relief followed the vomiting of 300 cc of bile-stained fluid. On February 26, by gastric lavage, 500 cc of dark green fluid were recovered. On February 27, lavage was attempted, but no fluid was recovered. Six hours later 800 cc of fluid were recovered and four hours later 600 cc

23 Dr C F Dixon will make a separate report of this case showing the effects of different forms of treatment on the carbon-dioxid combining capacity of the blood and chlorid content of the plasma.

gastric lavage, 10 cc of dilute hydrochloric acid by rectum twice daily, calcium chlorid 10 cc of 10 per cent solution twice daily, and fluids by rectum, 5 per cent glucose solution, were given. The condition continued to grow worse, and the patient died thirteen days after the onset of the obstructive symptoms (Table 8).

Necropsy revealed perforating chronic duodenal ulcer, posterior gastro-enterostomy and gastrostomy, acute toxic nephritis, terminal edema of the lungs with bronchopneumonia, arteriosclerosis and congestion of the brain. The short-loop gastro-enterostomy did not reveal leakage. The stoma admitted two fingers. The stomach was dilated, 2. In the posterior portion of the duodenum 5 cm below the pylorus, there was a small, partially healed ulcer, moderately indurated and firmly adherent to the pancreas, measuring 1 by 0.8 cm. The suprarenals and pancreas were normal, grossly. The kidneys weighed 175 gm each, the capsules stripped easily, the cortex was thickened and regular, the striae were indistinct.

TABLE 8—*Chemical Studies of the Blood, Gastric Contents, Urine and Spinal Fluid in Case 7*

Date	Blood						Gastric Contents		Urine Chlorids, Gm for Each Liter
	Urea, Mg for Each 100 C c.	Creatinin, Mg for Each 100 C c	Chlorids, Mg for Each 100 C c	Carbon Dioxid, Volume Percentage	Sodium, Mg for Each 100 C c	Potassium, Mg for Each 100 C c	Sodium, Mg for Each 100 C c	Potassium, Mg for Each 100 C c	
2/17/22	117		353	118		18.46	413	24	0.4*
2/20/22	235		445	125	306	15.9			0.3*
2/22/22	Gastrostomy								
2/24/22	192	6	653	94	351	14.9 15.19			0.2
2/24/22	Palmer hemoglobin 119								
2/27/22	Spinal fluid after death showed sodium, 405 mg for each 100 c c and potassium 12 mg for each 100 c c								

\* Acid

TABLE 9—*Chlorids in Necropsy Tissues*

Tissue	Wet Weight, Gm	Dry Weight, Gm	Water Extract, Gm	Chlorids, Mg for Each 100 Gm Fresh Tissue
Rectus muscle	5	1.3	3.7	120
Liver	5	1.25	3.75	256
Kidney	5			294
Brain	5	1.13	3.87	180
Lung	5	0.92	4.08	320
Heart	5	2.25	2.75	

There was an occasional sclerosed glomerulus in the kidneys, with atrophy of corresponding tubules and lymphocytic infiltration. Some of the remaining glomeruli were lobulated, and slight interstitial fibrosis was present. The tubules showed acute changes. The tubular epithelium was swollen, granular and extensively disintegrated. The nuclei were pyknotic or had disappeared. In many tubules the epithelium had disintegrated entirely. Many of the necrotic cells showed extensive deposits of calcium salts. The lumen of the tubule contained disintegrated cells, coagulated fluid and many casts. The condition was diagnosed as acute toxic nephritis by Dr. Robertson (Fig. 3). There was adipose replacement of the parathyroids (Table 9).

This patient had a typical history and roentgenologic findings of duodenal ulcer without obstruction. The operation revealed a large, adherent duodenal ulcer. A gastro-enterostomy was performed. Ten

Necropsy revealed diverticulum of the duodenum, possibly the result of an ulcer, marked dilatation of the stomach, toxic nephritis with terminal bronchopneumonia, and arteriosclerosis, 1 The right kidney weighed 135 gm and the left 130 gm The capsules stripped readily, leaving a smooth surface The cortices and medulla were clearly demarcated, and the cortical markings were fairly regular and distinct There was slight bulging of the columns of Bertini The stomach contained about 1,000 c c of sour, milky fluid Grossly, the mucosa was normal About 3 cm beyond the pylorus on the posterior superior surface was an outpouching of the duodenum about 3 cm in diameter and 3 cm deep The remainder of the duodenum and its contents were intact The upper 25 cm of the jejunum was injected

Histologic examination revealed many small areas of bronchopneumonia Lymph nodules were fairly prominent and relatively numerous in the spleen Marked calcium deposit was present in the cortex of the kidneys, and brownish pigment in the cells of the collecting tubules, the tubules contained many casts in the lumina The blood vessels were congested Granular changes were noted in the tubular epithelium Sudan III sections demonstrated that the epithelium of the convoluted and collecting tubules contained a large amount of fat

On this patient, who had a well defined clinical history of duodenal ulcer, a posterior gastro-enterostomy was performed Five days later, he developed intermittent obstructive symptoms Gastric tetany developed, with symptoms of duodenal intoxication, ending in death The chemical studies of the blood revealed the characteristic changes, that is, lowering of plasma chlorids and increases of the level of the non-protein nitrogen, urea, creatinin and increased carbon dioxide carrying capacity, also evidence of blood concentration

CASE 7 (A382714) —Mr A L B, aged 41, came to the Clinic because of epigastric pain of twenty years' duration, occurring two to three hours after meals, and relieved by food and alkali The attacks recurred once or twice annually and lasted three or four months A remission lasting three years occurred in one instance A history of obstruction could not be elicited

The hemoglobin was 75 per cent (Dare), the systolic blood pressure was 110 and the diastolic 70 The gastric contents showed a total acidity of 32 and free hydrochloric acid 22 Roentgenograms revealed a duodenal ulcer without obstruction

Surgical interference was advised on account of the chronicity of the lesion and operation performed A saddle ulcer, involving the upper margin of the duodenum and adherent to the pancreas, was found A posterior gastro-enterostomy was performed The postoperative convalescence was uneventful, and the patient was dismissed on the ninth day to the convalescence hospital On the tenth day, he complained of epigastric distress He vomited 240 c c of greenish fluid and was relieved The stomach tube was passed daily and varying amounts of thin, greenish, fluid were recovered On March 16, tonic contractions of the arms were present The patient complained of severe pains in the arms and in the epigastrium Two days later he became weaker and frequently vomited large amounts of the green, thin fluid The hands assumed the position characteristic of tetany, and there was one generalized convulsion The face, ears and hands were florid red The vomiting continued, and there was marked puckering of the mouth The patient was very restless, his extremities moved continuously The following day the condition remained the same, with symptoms of tetany becoming more marked An abdominal exploration was performed under local anesthesia, but obstruction was not found Gastrostomy was then performed From the onset, medical treatment including frequent

with relief of the distention distress. The patient continued in fairly good condition until the fifteenth day, when he was seized with a knife-like pain in the left axillary region which was aggravated by breathing, "catching his breath." Examination of the chest was negative. The temperature and pulse were normal. The leukocyte count was 9,100. On February 19, a similar attack of pain occurred, which was referred more to the epigastric region. The pulse rate was 120, and slight cyanosis was noted on the lips and tongue. Two thousand, five hundred cubic centimeters of gastric content were withdrawn, with relief from the pain. On February 20, 900 c.c. of fluid were withdrawn by gastric lavage. The respiration was 24, the pulse 88. The hemoglobin content was 80 per cent (Dale), erythrocytes, 4,970,000. Chvostek and Trousseau signs were negative. On February 21, the patient was in fair condition, respiration was 30, there was slight hyperpnea, the face, ears and hands were strikingly florid. Lavage was continued every four hours. Dilute hydrochloric acid was given by mouth, 30 minims every four hours, and calcium chlorid was administered by rectum, 10 c.c. of a 10 per cent solution twice daily. The urine showed a moderate trace of albumin, hyaline casts and erythrocytes. The patient's condition continued to improve, and no further retention was demonstrated by means of the gastric tube (Table 10).

TABLE 10—*Chemical Studies (Case 8)*

Date	Blood			Gastric Contents			Urine		Hemo- globin, Palmer Per centage
	Urea, Mg for Each 100 C c	Plasma Chlorids, Mg for Each 100 C c	Carbon Dioxid, Volume Per- centage	Sodium, Mg for Each 100 C c	Potas- sium, Mg for Each 100 C c	Chlorids, Mg for Each 100 C c	Potas- sium, Mg for Each 100 C c	Chlorids, Mg for Each 100 C c	
2/20/22	30	450	92						
2/21/22	31	428	93	355	19				
2/23/22	17	155	98						116
2/24/22						439	64	80	
3/ 1/22	20	610	68						

Intermittent Obstruction as Shown by Amounts of Gastric Contents in Vomitus and Lavage

	February 11	February 14	February 19	February 20	February 24
	240 C c	1,700 C c	1,600 C c	180 C c	100 C c
	600 C c	150 C c		2,500 C c	900 C c
				300 C c	
Total	840 C c	1,850 C c	1,600 C c	2,980 C c	1,000 C c

This patient had duodenal ulcer without obstruction. Five days following gastro-enterostomy he developed signs of intermittent obstruction. Early signs of gastric tetany were present. There was a definite increase of carbon-dioxid combining power of the blood and a moderate decrease of plasma chlorids. The condition was relieved before severe renal injury resulted. No urea retention was present. The urine showed evidence of renal irritation. Unfortunately no estimation of the phenolsulphonephthalein excretion was made.

CASE 9 (A91674)—Mr. T. D., aged 28, came to the Clinic on Sept. 9, 1913, complaining of atypical symptoms of gastric ulcer, consisting of occasional vomiting of sour, thick material, bloating and continual epigastric distress. There was no definite food relief, but the pain was most severe from two to three hours after meals. He had had one attack of hematemesis. A roentgen-ray examination revealed obstruction of the pylorus and ulcer of the duodenum. Examination of the urine was negative. The gastric contents after a test meal revealed a total acidity of 70 and free hydrochloric acid, 66.

days after operation, signs of duodenal obstruction with symptoms of gastric tetany developed. Exploration of the abdomen did not reveal the cause for the symptoms. The laboratory examinations gave evidence of marked renal insufficiency. The blood and urine chlorids were low, but following a relief drainage operation on the stomach the plasma chlorids returned to normal. An alkalosis was present. Normal values were obtained for sodium and potassium. The necropsy tissues showed chlorid depletion. The death in this case we believe can be explained on the basis of renal insufficiency, the duodenal stasis providing the toxic agent responsible for the injury. Necropsy demonstrated the existence of a severe toxic nephritis.

CASE 8 (A108879)—Mr. A. P., aged 33, came to the Clinic on May 27, 1920, complaining of having had gastric distress with marked periodicity for



Fig. 3 (Case 7)—Section of kidney showing areas of tubular degeneration and calcareous deposits in the tubules ( $\times 100$ )

ten years. The clinical history was typical of duodenal ulcer, with pain coming on about two hours after eating, worse at night and relieved by alkalis and food. He had been examined in the Clinic in 1914, and a diagnosis of duodenal ulcer made, but operation was refused. The patient was again admitted to the Clinic on Jan. 28, 1922.

Examination of the urine was negative. The blood contained 73 per cent (Dare) of hemoglobin and 4,150,000 erythrocytes. Gastric analysis revealed a total acidity of 32 and free hydrochloric acid, 20, the total amount recovered was 175 cc. The systolic blood pressure was 130 and the diastolic 80. Roentgenograms revealed duodenal ulcer without retention.

Operation was performed on Feb. 3, 1922. A duodenal ulcer 2 cm. in diameter was found within 1 cm. below the pyloric ring, but without obstruction. A posterior gastro-enterostomy was performed. The patient did very well until the fifth day when he vomited 140 cc. of bile-stained fluid. The tube recovered 600 cc. of thin, greenish fluid. The temperature and pulse were normal. On the eighth day, 1,700 cc. of thin, greenish fluid were vomited.

A gastro-enterostomy was performed for duodenal ulcer. Progressive gastric symptoms with evidence of intermittent pyloric obstruction developed. Six years later a second operation revealed a gastrojejunal ulcer which was excised. Obstructive symptoms with gastric tetany developed after operation with clinical and laboratory signs of renal injury. The patient recovered. Subsequent reports have shown complete subsidence of renal damage.

CASE 10 (A369991)—Mr. T. R., aged 45, came to the Clinic on Aug. 26, 1921, because of "rheumatic pains" in the legs. A gastro-enterostomy had been performed elsewhere five years before, because of vague epigastric distress. Since then the patient had had intermittent epigastric distress, with vomiting and upper abdominal distention. For the last five months he had noted numbness, aching and cold sensations in the feet, and slight tingling in the fingers. He had lost 15 pounds (6.8 kg.) in weight.

The fractional gastric analysis showed achlorhydria, the total amount recovered being 435 c.c. The urine contained a trace of albumin. The hemoglobin content was 73 per cent (Dare), and there were 4,190,000 erythrocytes. The

TABLE 12—Findings in Case 10

Date	Blood		Plasma Chlorids, Mg for Each 100 C c	Sodium, Mg for Each 100 C c	Potas- sium, Mg for Each 100 C c	Calcium, Mg for Each 100 C c	Gastric Chlorids Mg for Each 100 C c	Urine
	Urea, Mg for Each 100 C c	Carbon Dioxid, Volume Percentage						
9/ 3/21	255	98	285					
9/14/21	264	93	240					
9/15/21	260	88	290	361	4	7.2		Acid
9/16/21	268	93	293	369	4			
9/17/21	403	72	370				369	0.12 gm chlorid

roentgen ray revealed retention 3. A diagnosis was made of chronic pyloric obstruction with possible gastric tetany.

The patient was hospitalized for preoperative treatment consisting of gastric lavage and the forcing of fluids. The amount of gastric contents obtained by lavage ranged from 500 to 1,000 c.c. The night preceding the date set for operation the patient became unconscious and had convulsive twitchings. These symptoms became more severe and convulsions and mania developed. The hands assumed the tetany position. Chvostek and Trousseau's signs were positive. The treatment consisted of frequent gastric lavage with recovery of large amounts of contents. Calcium chlorid was given intravenously. On the sixth day, a left parotitis developed. The patient's condition became gradually worse and a shocklike state supervened, evidenced by low blood pressure, and red face and ears, suggesting dehydration. Weakness increased, and the patient died in coma (Table 12).

Necropsy revealed ancient gastroduodenostomy with obstruction and permanent dilatation of the stomach and duodenum, bilateral coalescing bronchopneumonia, toxic nephritis, chronic right seminal vesiculitis, ancient tuberculosis of the right lung, and slight arteriosclerosis of the aorta.

The mucosa of the duodenum was deeply congested and almost gangrenous. No evidence of ulceration in the stomach was found, and the duodenum was widely patent. The left and right kidneys weighed 210 and 185 gm., respectively. The capsules stripped, leaving a smooth surface. The surfaces appeared moist. The cortical markings were indistinct. The glomeruli were visible as yellowish points.



On Sept 17, 1913, a posterior gastro-enterostomy and an appendectomy were performed. Recovery was uneventful. The patient was again examined in the Clinic on March 20, 1919. He had felt fairly well after the operation, but he still had some gastric distress on overeating, indefinite bloating and a "tired feeling" in the stomach. He belched sour material, but he did not vomit. He said he thought his stomach was "closing up." Physical examination showed nothing of importance. The systolic blood pressure was 120, and the diastolic 70. Roentgenograms of the stomach revealed a gastrojejunal ulcer. Urinalysis was negative. A gastric test meal gave a total acidity of 30 and free hydrochloric acid, 20. The surgeons advised against operation because symptoms did not warrant it.

On May 17, 1919, the patient returned the third time because of more marked bloating, nausea and vomiting of green, watery fluid. He had lost 17 pounds (7.7 kg) in weight in six months. The urine showed a specific gravity of 1.020 with a trace of albumin. Three days later albumin 2 and hyaline casts 3 were noted. Roentgenologic examination revealed a gastrojejunal ulcer with retention 1.

At operation on June 6, a gastrojejunal ulcer was found and excised. Until the seventh day the patient convalesced uneventfully, then he developed mild

TABLE 11—*Findings in Case 9*

Date	Urine			Blood			Urea, Mg for Each 100 C c	Remarks
	Specific Gravity	Albu- min	Casts	Hemo- globin, Per centage	Erythro- cytes	Leuko- cytes		
3/20/19	1.014			76				
5/27/19	1.020	1						
5/30/19	1.010	2	3 hyaline					
6/11/19	1.025	3	3 hyaline 1 granular	87	5,440,000	12,900	120	Operated 6/4/19 Vomiting, marked fluid loss, signs of tetany
6/17/19	1.012	2	2 hyaline 1 granular					
6/23/19							101	
10/14/19	1.026	1		80				General condition good, slight pain in arms and legs

obstructive symptoms. He complained of stiffness in the hands and feet. His face and mouth felt numb, his legs were cramped and his toes became flexed. He had pain in the side and back. Gastric lavage was given every six hours, the amounts of thin green fluid recovered averaging about 1,000 cc. Proctoclysis, 10 cc of 5 per cent solution of glucose in 240 cc of sodium chloride solution and sodium bicarbonate were given. The patient was having definite spasms of tetany, the hands assuming the typical position. His general condition was not alarming. On June 13, gastric lavage returned clear. Ten hours later 150 cc of greenish fluid were recovered. The specific gravity of the urine was 1.012, the albumin was 2 and the hyaline casts 2. The urea content of the blood was 120 mg for each 100 cc. The hemoglobin content (Dare) was 87 per cent, the erythrocytes 5,440,000 and leukocytes 12,900, polymorphonuclear neutrophils 78.5 per cent and small lymphocytes 21.5 per cent. On June 14, the patient complained of numbness in the hands and feet at the time of the lavage and said he would have a spasm if this were continued. On June 23, the blood urea was 101 mg for each 100 cc. Treatment was continued. On July 2 the condition cleared up entirely and at the last report the urine showed a faint trace of albumin. After the patient recovered he said that for the past ten or twelve years he had had periods of gastric distress associated with numbness, quivering of the lips and twitching of the abdominal muscles (Table 11).

Extensive adhesions had produced kinking of the proximal loop, and the bowel was twisted and turned to the right. An entero-anastomosis of the proximal loop to the distal loops was quickly made. The postoperative convalescence was uneventful, and the patient was dismissed cured.

This patient represents a rather mild condition of "duodenal intoxication." As this case was an early one in our series, the importance of renal functional studies was not appreciated. The urinalysis showed definite evidence of renal irritation. The early operative relief of the obstruction prevented the further development of renal injury. The alkalosis was definite.

#### DISCUSSION OF CLINICAL FINDINGS AND LABORATORY DATA

*Etiology*—The eleven cases herein reported present a clinical syndrome supposedly typical of duodenal intoxication. Symptoms, probably those of gastric tetany, were present in all but one of the cases. Etiologically two types were represented,<sup>24</sup> those with demonstrable mechanical obstruction, and those without. We assume the latter to be due to functional stasis or a dynamic, or possibly intermittent obstruction. The cases in the first group included those of obstruction due to pyloric or duodenal ulcer, carcinoma, gastrojejunal ulcer and adhesions, those in the second group presented symptoms identical with those in the first, but adequate cause for obstruction could not be found by exploratory or necropsy examinations. The condition may be analagous or related to that in paralytic ileus. In this connection the cause of vomiting should be considered. The possibility of a toxic substance originating in the obstructed duodenum and stimulating the vomiting center cannot be ignored.

*Gastric Symptoms*—The gastric symptoms were definite in both groups. Vomiting, although not invariably persistent, was present in all cases. In the chronically obstructed group, there were intermittent crises every few days with vomiting and the recovery of large amounts of thin, serous fluids. The emptying of the stomach was always followed by relief from symptoms for variable periods. In the post-operative group with acute obstructive symptoms, relief was less pronounced. The fluid loss in the gastric secretion varied from 600 to 6,000 cc in twenty-four hours. Epigastric pain was not a feature. Usually the patients complained only of mild distress in the epigastrium or of distention, which was relieved by belching or vomiting. The sharp colicky pains of lower intestinal closure were lacking. Nausea was usually absent.

*Nervous Symptoms*—In our experience, in fatal cases, tetany or tetany-like symptoms usually developed in the course of toxemia. The

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<sup>24</sup> Renal injury from alkaline treatment of ulcer was not encountered in this group of cases except, possibly, in Case 2.

Histologic examination revealed many casts in the tubules of the kidneys, foci of calcareous deposit and many foci of lymphocytic infiltration. Several epithelial crescents were seen in the glomerular cavity. The stroma was edematous (Table 13).

This patient had had a gastro-enterostomy performed elsewhere five years before. Symptoms developed resembling those of gastric tetany. The gastric symptoms were not marked at the time of examination. The clinical condition proceeded to that known as "duodenal intoxication." The tetany features of the case were marked. Later symptoms suggestive of uremia developed, associated with laboratory evidence of marked renal insufficiency. The necropsy examination confirmed the diagnosis of toxic nephritis.

CASE 11 (A353616)—Mrs. T. B., aged 31, came to the Clinic on March 28, 1921, complaining of persistent loss of weight and strength. She had had periodic attacks of migraine. A gastro-enterostomy had been performed elsewhere in September, 1920, on the roentgenologic evidence of ulcer. Clinical evidence was lacking. For the first five days after the operation, the patient vomited large amounts of greenish, watery gastric contents. Following lavage the patient was free from gastric distress until three months later when

TABLE 13—*Determination of Chlorids in Necropsy Tissues (Case 10)*

	Mg for Each 100 Gm Fresh Tissue
Brain	220
Wall of stomach	216
Liver	172
Muscle	80*
Kidney	208

\* Probably low, difficult to extract

obstructive symptoms, severe gas pains, nausea, marked loss of weight and strength, and frequent vomiting appeared almost daily.

The patient was emaciated and had a ventral hernia at the site of the operative scar. Her weight was 85 pounds (38.5 kg). The systolic blood pressure was 85. Urinalysis showed specific gravity of 1.016, albumin 2 and an occasional hyaline cast. Examination of the blood revealed hemoglobin, 80 per cent (Dare), erythrocytes, 5,120,000, and leukocytes, 7,600. Roentgenograms of the stomach disclosed a large stomach with retention 2. A gastric meal showed a total acidity of 14 with free hydrochloric acid 8. 460 c.c. of contents were recovered.

The patient was hospitalized for preoperative treatment. Following gastric lavage and proctoclysis the vomiting was controlled and she gained 6 pounds (2.7 kg) in weight. The stomach tube recovered 650 c.c. with some food remnants but no bile. The patient complained of numbness and twitching sensations in the hands and feet, particularly during the gastric tests. This was relieved by the aspiration of large amounts of the gastric contents. One definite attack of gastric tetany occurred with characteristic position of the hands, and thickness of speech. The Chvostek and Trousseau signs were present. The stomach was definitely distended, and 1,000 c.c. of greenish fluid were withdrawn, after which there was marked relief of the symptoms. The carbon dioxide combining power was 110. Operation was performed on April 26. The pylorus was opened, but there was no evidence of previous ulcer of the stomach or duodenum. The stoma was large, admitting three fingers

was definitely established, the acid-base balance was always disturbed, as demonstrated by an increase of the carbon dioxide combining power of the blood<sup>28</sup> Murray<sup>29</sup> has found unchanged or only slightly changed values in the hydrogen-ion concentration of the blood in experimental closure of the pylorus. This change in the acid-base equilibrium is probably due to excessive loss of acid in the gastric juice which may be an exaggerated phase of the normal carbon dioxide curve after meals. McCann<sup>10</sup> has observed experimentally that reestablishment of gastrojejunal continuity causes a decided decrease in the alkaline reserve of the blood. We noted a similar response in Case 7, following a drainage relief operation. It appears feasible, at least, that the loss of the hydrogen-ion in the gastric juice results in a relative increase of the blood bases. Chloride depletion was observed early, and remarkably low values were observed in the blood plasma. An increase of plasma chlorides was observed in Case 7 as a result of reestablishment of gastrojejunal continuity. The chloride depletion is probably due to loss of chlorides in the gastric juice. In only one instance was the increase of sodium in plasma found. The chloride content of the tissues showed that an actual depletion existed and that fixation of chlorides, as in pneumonia, was not present. The chloride values showed a relatively early change after the toxemia was established, and as noted in two of the patients, followed shortly after the disturbance in the alkaline reserve.

High levels for nonprotein nitrogen in the blood were observed in all our severe cases. High values were obtained for urea in the blood and corresponding increases in creatinin. Definite changes were noted in the acid-base balance and chloride level in several cases in which stasis was relieved before the renal injury had progressed sufficiently to produce azotemia. We believe that while tissue destruction (catabolism) may be excessive, renal injury is an important factor. In cases in which the phenolsulphonephthalein test was given, the excretion of the substance was definitely decreased. The renal injury was grave, as shown by functional tests and necropsy examinations. Clinically, the renal lesion suggested a degenerative type similar to that so frequently seen in many forms of experimental nephritis. Edema, increased blood pressure and retinal changes were absent.

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28 Van Slyke has shown that the alkalosis is due to an alkali excess since the bicarbonate-carbonic acid ratio is disturbed in favor of the bicarbonate. When the hydrogen-ion concentration of the blood is undisturbed, he has designated the condition as a "compensated alkalosis."

29 Murray, H. A. The Bicarbonate and Chloride Content of the Blood in Certain Cases of Persistent Vomiting, *Proc Soc Exper Biol & Med* **19** 273-275 1922

symptoms referable to heightened nerve irritability may be either motor or sensory in character. Several patients with chronic obstruction complained for years of vague pains and paresthesia, particularly in the extremities, during which the gastric symptoms were insignificant. Pain, tingling and twitchings of all degrees may be present. In acute cases (Case 8) the pain may be severe and simulate an acute inflammatory lesion. Spasmodic and convulsive stages of tetany were seen in the more severe toxemias and often represented terminal events. In this stage, we found evidence of renal injury and insufficiency.

*Shock-like Features*<sup>25</sup>—The shock-like features of the syndrome may be related to the marked fluid loss, resulting from persistent vomiting. The low blood pressure, red facies,<sup>26</sup> high hemoglobin, asthenia, and low muttering delirium, denoted the severity of this fluid depletion. Maintenance of blood fluids is often impossible at this time. Keith has pointed out that in shock the vessel walls lose the capacity to retain fluids.<sup>27</sup> This condition apparently obtains also in some cases of duodenal toxemias. In seven of our cases, fluids were administered, such as salt and glucose solutions, in large amounts without demonstrable improvement. Transfusions or colloidal solutions were not employed.

*Urinary Excretion*—The urine was usually scanty as a result of excessive loss of fluid from the stomach. The urine clots were greatly diminished. The concentration and dilution functions of the kidney were not definitely impaired in one case in which they were studied. Albumin, casts, and red blood cells were always found in the urine in the toxic stage.

*Blood Chemistry*—The chemical changes in the blood and tissues were practically pathognomonic and are consequently of great diagnostic and prognostic significance. The decrease in plasma chlorids and the increase in the carbon dioxide combining power of the blood appeared first early in the development of the toxemia. When tetany

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<sup>25</sup> Gerard has recently compared the pharmacologic action of "obstruction fluid" and histamin. The shock features of duodenal toxemia and histamin poisoning are, in many respects, similar.

<sup>26</sup> One of us (L.G.R.) has previously noted this red facies in patients with diabetes insipidus, to whom histamin was administered.

<sup>27</sup> Keith has also produced experimental dehydration in dogs by injecting intravenously a calculated amount of 50 per cent saccharose solution. By this method a marked diuresis accounted for an average loss of 11 per cent of the body weight in a few hours. Definite and constant circulatory changes occurred during the period of dehydration. These were characterized by increased blood viscosity, raised hemoglobin concentration and a distinctly diminished circulating plasma volume. Shocklike features were not present. With the giving of an adequate amount of water by mouth, the circulation was rapidly restored to normal.

festations of tetany or shock. The findings of increased carbon dioxide combining capacity of the plasma with low plasma chlorids indicate the existence of this toxemia. And when this is associated with evidence of renal insufficiency, as shown by increased blood urea with low phenolsulphonephthalein excretion, the diagnosis can be made with certainty. The extent of the damage is reflected in the degree of chemical disturbance.

*Prognosis*—The preoperative and postoperative cases should be considered separately. In the preoperative group, the nature of the pathologic lesion is of paramount importance. The alkalosis is secondary, is of less consequence and more easily controlled. Aside from the alkalosis, chlorid depletion and renal insufficiency may be present and yet recovery be possible (Case 2). Had operation been undertaken in the presence of these findings to the neglect of preoperative medical treatment, the outcome would probably have been fatal. In determining the operative risk, the degree of renal involvement is important. Under the proper management, renal function may be reestablished in this condition, as happens quite frequently following relief of lower urinary tract obstruction. No sharp line of division can be drawn between the operative and nonoperative cases, but an attempt to improve renal function by suitable medical measures should be undertaken prior to operation. Palliative operations involving drainage may be desirable. A blood urea above 100 mg for each 100 cc and a phenolsulphonephthalein excretion of 10 per cent or less represents a poor surgical risk.

The postoperative cases are likely to prove more serious. The onset as a rule is more acute, the course more fulminating and death may occur before the seriousness of the condition is recognized. Relief of stasis may result in recovery if effected by either medical or surgical treatment before serious renal damage occurs. In both groups, the degree of renal injury is probably the determining factor. The advent of general convulsions or severe manifestations of tetany also indicate grave prognosis.

*Treatment*—Obviously, in view of the obstructive origin of the toxemia the treatment is primarily surgical. The relief of the obstruction is the main objective, and consequently simple drainage operations may be desirable. When, however, surgical measures are associated with excessive risk, medical treatment may be necessary. In surgical interference, etherization is undesirable. According to the work of Dale<sup>32</sup> in histamin poisoning, resistance is markedly lowered by ether. On this basis, Gerard advocates the use of nitrous oxid and oxygen.

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32 Dale, quoted by Gerard

*Pathologic Condition*—In the six cases ending fatally, pathologic examinations showed severe toxic nephritis<sup>30</sup> The tubular epithelium revealed degenerative changes Granular and fatty degeneration were uniformly present No marked changes were seen in the glomeruli When calcium had been administered as a therapeutic measure, deposits of this substance were found in the tubular epithelium This is of interest in connection with the work of Bowler, who finds that excessive doses of calcium chlorid produce no toxic effect on the kidneys<sup>31</sup> The urine contained albumin, casts and erythrocytes during the toxic stage Marked dilatation of the stomach and duodenum were noted in all necropsy cases Definite changes in the duodenal mucosa were seen in one case only (Case 10) The absence of gross pathologic changes in the mucosa does not militate against the assumption of Hartwell and others that changes in this tissue are an essential feature of the toxemia Minor or functional changes may exist

*Correlation of Clinical and Laboratory Data*—It is difficult to determine to what extent certain symptoms are due to renal insufficiency or tetany Uremia is characterized chiefly by symptoms referable to the gastro-intestinal and nervous systems and by asthenia Such symptoms are present in duodenal toxemia Our impression, perhaps without sufficient basis, has been that the earlier symptoms of this character were due to tetany In the later stages, in the presence of proved renal insufficiency, we believe that the symptoms are at least partially uremic in origin Such symptoms are daily encountered in cases of nephritis in the absence of tetany and even in the presence of acidosis The renal injury may be present fairly early after the onset of the toxemia Headaches are common The mental aberration particularly suggests uremia Consequently, we believe that the burden of proof should rest on those who hold that these symptoms are not uremic in origin

The pathologic condition in the kidney is in keeping with the clinical and laboratory data The rôle of the kidney cannot be disregarded, since the renal lesion is often the most outstanding pathologic finding at necropsy

*Diagnosis*—In the diagnosis of duodenal intoxication, the laboratory findings are of great importance and sometimes pathognomonic In cases of duodenal ulcer with obstruction, vomiting is frequent, in both preoperative and postoperative stages When, however, vomiting is marked or persistent, chemical studies of the blood are indicated, and especially when the vomiting is accompanied by florid facies and mani-

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30 There was no evidence that a preexisting nephritis had been present in the cases coming to necropsy, differing in this respect from the cases reported by Tucker

31 Personal communication

blood, by decreased renal function, and in case of death by pathologic changes in the kidney

3 The clinical picture consists of (1) vomiting of large amounts of a thin, serous, bile-stained fluid, (2) evidences of dehydration, red florid complexion, high hemoglobin, low blood pressure and asthenia, (3) by tetany-like manifestations, and (4) features of shock and uremia

4 The blood shows (1) a low level of chlorids, (2) a high carbon dioxid carrying capacity, and (3) a high level of blood urea and of creatinin

5 Urinalysis reveals albuminuria and casts

6 Renal functional studies indicate renal insufficiency, high values for urea and creatinin, and a decreased excretion of phenol-sulphonephthalein

7 Necropsy in six cases revealed the pathologic condition of nephrosis characterized either by acute degenerative changes in the tubular epithelium or by a diffuse nephritis

8 Prognosis and treatment are discussed



Medical treatment may be considered under the heading of (1) drainage or mechanical relief, (2) administration of fluids, (3) dietary control, and (4) drug therapy. Drainage can be obtained by means of the stomach tube. Frequent lavage is essential. Dilute hydrochloric acid, 1 to 2 c c, may be given through the stomach tube. When tetany exists, calcium chlorid 10 per cent solution in doses of 1 to 2 gm may be given in this manner or intravenously. Since excessive fluid is lost by vomiting and concentration of the blood results, large amounts of water are indicated. This can be administered in the form of physiologic saline solution intravenously, subcutaneously, or by rectum. Dragstedt has found that Ringer's solution is more effective than sodium chlorid solution in controlling experimental tetany. It proved of great value in one of our cases. Accumulation of nitrogen in the blood indicates a low protein and high carbohydrate diet. We have used farinaceous food and milk, to which lactose and cream have been added. Since the putrefactive bacteria flourish in an alkaline medium and, the aciduric flora in an acid medium, buttermilk, or *Bacillus acidophylus* milk may be tried.

Drugs are used to combat alkalosis and tetany. Dilute hydrochloric acid is given in 2 to 4 c c doses in sodium chlorid solution by rectum, or by mouth if obstruction is not complete. Five hundred cubic centimeters of 0.1 normal hydrochloric acid in 500 c c of physiologic saline solution has been used by Murray. Haldane<sup>33</sup> has recently shown that ammonium chlorid when given by mouth produces a decrease in the alkaline reserve of the blood and alveolar carbon dioxide<sup>34</sup>. In the light of recent knowledge on the toxicity of sodium bicarbonate, it is important to avoid it in gastric tetany and duodenal toxemia. In the medical treatment of duodenal ulcer, the condition of the kidney constantly followed nephritis, for Hardt and Rivers have shown that toxic symptoms appear at times within the first week of treatment before neutralization of the gastric juice or alkalinization of urine is effected.

#### SUMMARY

1 Eleven cases are reported in which as the result of organic obstruction, anatomic or physiologic stasis in the duodenum, duodenal toxemia developed.

2 Duodenal toxemia is characterized by a clinical syndrome, by urinary changes, by pathognomonic changes in the chemistry of the

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33 Haldane, J. B. S. Experiments on the Regulation of the Blood's Alkalinity, *J. physiol.* 55 265-275 1921.

34 McCann has given this method clinical trial in a case of gastric tetany, using 500 c c of an 0.822 per cent solution of ammonium chlorid (hydrogen-ion concentration 7). The solution was previously tested for hemolysis against patients' blood. Tetany symptoms were relieved.

smaller is 1.82 grains (0.1 gm), and it would be necessary to assume absorption of approximately one half of one of the larger tablets or a corresponding number of smaller ones to explain death from this source. On the contrary, there are some patients who recover in spite of having apparently retained much more than the estimated minimum lethal dose. It is always, however, impossible to know how much mercury may have been removed and how much may have been rendered inert by material in the gastro-intestinal tract and passed out unabsorbed.

Mercuric chlorid poisoning furnishes an excellent opportunity to study the retention of nitrogenous waste products in the blood, and several such studies have been made<sup>2</sup> and the findings compared with those seen in other kidney lesions. Myers and Lough,<sup>3</sup> in their studies on nephritis, have emphasized particularly the prognostic value of the blood creatinin figures and have stated that figures of 3 to 5 mg per 100 cubic centimeters are decidedly unfavorable and that amounts above 5 mg probably mean early fatal termination. They have reported a fatal case showing creatinin, 33.3 mg per 100 cubic centimeters of blood, urea nitrogen, 240 mg, and uric acid, 15 mg. Campbell,<sup>4</sup> on the other hand, believes that creatinin retention as a guide in prognosis is valuable only in chronic cases of kidney disease, and he cites one case of mercuric chlorid poisoning in which creatinin reached 12.5 mg and recovery occurred. Underhill<sup>5</sup> reported recovery of a patient after urea nitrogen reached 240 mg.

Rosenbloom<sup>6</sup> reviewed the previous literature on the therapeutic measures and suggested a method of treatment which seems to combine the more effective measures of the various methods previously used. For the benefit of those who are not familiar with it, we would refer to the original article. The treatment includes the use of calcium sulphid, sodium phosphate and acetate, intravenous injection of Fischer's solution, colonic irrigations, hot packs, alkaline drinks and proctoclysis of potassium acetate, sodium bicarbonate and glucose, rest in bed, etc.

This treatment has been used in our service with comparatively little modification for the past eighteen months, and has seemed to give the most favorable results. It combines many of the measures previously

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2 Elwyn, H., and Flood, E. P. Kidney Function in Case of Bichlorid Poisoning, *Med Rec* **98** 56 (July 10) 1920.

3 Myers, V. C., and Lough, W. G. The Creatinin of the Blood in Nephritis. Its Diagnostic Value, *Arch Int Med* **16** 536 (Oct.) 1915.

4 Campbell, W. R. Observations on Acute Mercuric Chlorid Nephrosis, with a Report of Two Cases, *Arch Int Med* **20** 919 (Dec.) 1917.

5 Underhill, A. J. Blood Urea in Renal Conditions, *New York M J* **102** 662 (Sept 25) 1915.

6 Rosenbloom. Acute Bichloride of Mercury Poisoning Treated by Newer Methods, *Am J M S* **157** 348 (March) 1919.

# A CLINICAL REPORT ON ACUTE CASES OF MERCURIC CHLORID POISONING \*

L C GATEWOOD, M D  
AND  
ARTHUR F BYFIELD, M D  
CHICAGO

Poisoning by mercuric chlorid is a condition of comparatively frequent occurrence at the present time, and the opportunity to study a considerable number of such cases has furnished data which seem of sufficient interest to justify a report. While some of these patients have been transferred to other hospitals within a comparatively short time after admission to the service, there have been a number which we have been able to study with a fair degree of thoroughness, and these have presented interesting findings.

Most of the work previously reported has been along therapeutic lines and has in the main tended to confirm the earlier general impression of a high mortality from this condition. Sansum<sup>1</sup> has reviewed particularly carefully the literature on the subject and has conducted animal experiments which seem to show that for dogs the minimum lethal dose is quite uniformly 4 mg of mercuric chlorid intravenously per kilogram of body weight. A dose of 5 mg per kilogram of body weight would quite regularly produce death with anuria, and his experiments tended to show that when anuria had been so caused, all attempts to reestablish the flow of urine by use of diuretic solutions failed. His figures correspond with those of various textbooks which give 3 to 5 grains (0.19 to 0.32 gm) as the lethal dose for an adult. It is quite impossible to confirm these figures clinically, since it is frequently impossible to know the dose which has been taken and equally impossible to know the amount which has been removed by vomiting, gastric lavage and catharsis. It is probable that some persons are much more susceptible than others. This is suggested particularly by the considerable number of cases of poisoning recently reported as due to absorption from the vagina, either from douches of mercuric chlorid solution or from tablets placed in the vagina to prevent conception. The amount of mercuric chlorid used in this way is, as a rule, small. There are two sizes of tablets commonly sold for antiseptic purposes—the larger one is 7.8 grains (0.5 gm) and the

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\*From the medical service of the Cook County Hospital. Read before the Chicago Society of Internal Medicine, May 29, 1922.

1 Sansum, W. D. Principles of Treatment in Mercuric Chlorid Poisoning, J. A. M. A. 70:824 (March 23) 1918.

One patient (M K) who left the hospital at the end of fourteen days very much improved, died at her home within two or three days under circumstances which suggest that she had probably taken a

TABLE 2—*Results with Rosenbloom's Method of Treatment and Former Methods of Treatment in Authors' Cases*

C case No	Age	Previous Health	Dose of Mercuric Chlorid	Mercury in Stomach Contents	Vomit-ing	First Treat-ment	Entered Hos-pital	Treat-ment	Days in Hos-pital	Result
723406 M K	24	Good	15.6 gr	—	15 min	Imme- diately 30 min	2 hr	G	2	Improved (Rel)
726604 G J	22	Good	20 gr	—	30 min		1 hr	G	10	Recovery
729561 K R	28	Good	?	—	No	1 hr	3 hr	G	3	Recovery
733012 A N	28	Pregnant	30 gr	—	15 min	1 hr	1 hr	G	5	Improved (Rel)
738267 L R	26	Pregnant	15.6 gr	—	No ?	2 hr	2 hr	G	1	Rel
739329 R M	20	Good	1.8 gr	—	15 min	15 min	15 min	G	1	Rel
738595 V K	24	—	30 gr ?	—	15 min		1½ hr	G	1	Rel
743400 A O	22	Alcoholism	?	—	Soon	?	?	G	—1	Rel
743782 J O'B	21	Poor	4 tabs size ?	—	Imme- diately	—	1 hr	G	—1	Rel
750145 N R B	24	—	7 tabs	+	10 min	10 min	45 min	R	16	Recovery
750976 V S	22	Good	?	+	10 min	—	1 hr	R	10	Recovery
753485 E B	28	—	10 tabs	+	No	—	2 hr	R	7	Recovery
755155 S S	20	—	6 tabs size ?	+	—	20 min	30 min	G	2	Rel
758244 J B	29	—	Bottle of tablets	+	Soon	Many hours	5 days	G	3	Died
764043 L O'R	40	—	40 gr	+	30 min	30 min	7 hr	G	3	Improved (Rel)
764448 R M	19	Skin lesion on leg	?	+	No	?	Many hours	G	4	Improved
766305 J S H	41	Good	?	++	—	30 min	4 hr	R	4	Rel, im- proved
766586 M I	40	—	11 tabs size ?	+++	4 hr	—	28 hr	R	13	Died
766759 M K	40	—	?	++	30 min	30 min	1½ hr	R	14	Recovery
766980 O M	29	25 tabs size ?	25 tabs size ?	+++	Few min	30 min	1 hr	R	36	Recovery
772721 F L	21	Syphilis	4 tabs	+	30 min	30 min	5 hr	R	13	Recovery (Rel)
773174 A S	62	Diabetes, morph nephritis	5 tabs	+++	Imme- diately	—	3 hr	R	8	Improved (Rel)
777363 E G	—	Good	5 tabs	+	30 min	30 min	1 hr	R	7	Recovery
784846 L B	22	Good, alco- holic	?	+++	30 min	30 min	1½ hr	R	12	Recovery
785329 O S	18	Mental dis	6 tabs	+	Few min	30 min	1½ hr	R	14	Recovery, trans to psycho
785439 O H	16	Good	1 tab	Tr	15 min	15 min	4 hr	R	14	Recovery
787296 H D	21	Pyelitis, gynecol	3 tabs 23.4 gr	++	10 min	30 min	24 hr	R	9	Recovery, trans to psycho

G indicates general methods of treatment formerly in use, R, method of treatment outlined by Rosenbloom, Rel, released to the care of relatives or friends. Such patients were usually transferred to private hospitals for further care.

further dose of poison after leaving the hospital, but definite information on this point was not obtainable. Since that time it has become our practice to have all such patients examined by the psychopathic department before discharge.

used and thus involves a considerable amount of time and effort. Lavage is continued until the washings are reported free from mercury. If this method has advantages over those previously used, they are probably dependent on the amount of mercury removed by the repeated lavage, as shown in case records contained in the tables. In one such case, mercury was found in the washings as late as eleven days after being taken and was present in considerable quantities during the early days of treatment. It is probable that a good deal of mercury is removed in this way, and it is to be hoped that later we may have quantitative determinations of the mercury so removed. To date this has not been possible.

From Jan 1, 1920, to May 1, 1922, there have been admitted to the Cook County Hospital to all services a total of seventy-one cases of mercuric chlorid poisoning, distributed as shown in Table 1.

TABLE 1—*Cases of Mercuric Chlorid Poisoning at Cook County Hospital from Jan 1, 1920, to May 1, 1922*

	Total	Recovered	Died	Mortality Percentage
1920	26	24	2	7.7
1921	35	28	7	20.0
1922	10	8	2	20.0
Total	71	60	11	15.5

Of this number, thirty have been admitted to our service. The results are shown in Table 2.

It will be noted that all cases in this series from No. 750145 to the end of the table showed positive tests for mercury in the stomach contents or urine or both. Prior to January, 1921, such examinations were not available, but only unquestioned cases have been included in the series. It has at times happened that patients have feigned poisoning with mercuric chlorid, but any such cases have been carefully excluded. When such cases arise they should be treated as cases of mercuric chlorid poisoning until repeated tests have demonstrated that no mercury is present, since it is also not unusual for one who has taken mercuric chlorid to deny it vigorously until told that chemical examination of the stomach contents reveals the poison.

Two of the patients in the twenty-seven cases here tabulated died in this hospital. Twelve of these patients were brought into the County Hospital as emergency cases and were transferred to other hospitals when friends or relatives became cognizant of their presence in the hospital. In this way a number of patients have been lost to observation before a sufficient period has passed to enable us to be certain of the outcome.

CASE 2—Carrie M (No 766980), aged 29, weight approximately 150 pounds (68 kg), was admitted to the hospital on July 20, 1921, at 5 p m. She had swallowed twenty-five mercuric chlorid tablets at 4 p m, and within thirty minutes milk had been given and vomiting induced. On entering the hospital she continually vomited blood streaked material which gave a strong test for mercury, and mercury was found in the stomach washings each day up to and including the sixth day. A trace of mercury was found in the urine as late as the fourteenth day. From the outset the patient was unable to void, and no urine was obtained on catheterization. The first urine was obtained on the seventh day, and from that time steadily increasing quantities were passed, although some of the first specimens were lost in expelling enemas, and it was impossible to obtain reliable data concerning the twenty-four hour output. The nitrogen retention reached its maximum on the eleventh day, as shown in the tabulated blood chemistry determinations, and from that time improvement was rapid. The patient remained in the hospital for thirty-six days and left the hospital apparently entirely recovered. She has been out of the city most of the time during the past year but has reported that urinalysis showed no abnormality and that she has been in good health.

TABLE 5—*Blood Chemistry in Case 2*

	Day							
	First	Third	Eleventh	Fifteenth	Nineteenth	Twenty-Second	Twenty-Seventh	Thirty-Third
Urea nitrogen	22.41	40.00	70.05	64.91	40.62	22.54	18.21	17.02
Urea	49.95	85.60	149.80	136.96	86.92	48.33	38.96	26.42
Uric acid	4.21	4.21	12.50	9.71	5.15	2.45	2.11	2.31
Creatinin	3.75	3.90	13.10	11.27	3.33	1.87	1.55	1.49
Sugar	191	97	95	141	—	—	—	—

TABLE 6—*Urine Examinations*

Day	Color	Specific Gravity	Reaction	Albumin	Sugar	Blood	Leuko-cytes	Casts	Remarks
7	Straw	?	Alkaline	0	0	0	+	0	3 c c only
11	Straw	1.009	Alkaline	0	0	0	0	0	
13	Straw	1.010	Alkaline	0	0	0	0	0	
14	Straw	1.014	Alkaline	++	0	0	0	0	
15	Straw	1.010	Alkaline	++	0	0	0	0	
20	Straw	1.010	Alkaline	Trace	0	0	+++	0	
25	Amber	1.010	Alkaline	0	0	0	++	0	
26	Amber	1.011	Acid	0	0	0	+++	0	
27	Straw	1.012	Acid	0	0	0	++	0	
32	Straw	1.012	Alkaline	0	0	0	0	0	
34	Amber	1.011	Acid	0	0	0	+	0	

CASE 3—Olga S (No 785329), aged 18, who weighed approximately 125 pounds (56.6 kg), was admitted to the hospital on Jan 20, 1922, at 12 10 a m, having swallowed six tablets (size unknown) of mercuric chlorid at 10 30 p m. One half hour after taking poison, she drank milk and vomited. Chemical examination revealed mercury in the stomach washings on the first, second and third days, and in the urine up to the fourth day. The patient was put at once on the Rosenbloom treatment as outlined, and made an uneventful recovery from the poisoning, being transferred on the fourteenth day to the Psychopathic Hospital for further observation because of a psychosis. This patient showed albumin and casts persistently present in the urine. No history of previous kidney disease was obtained. It is interesting to note that albumin and casts are by no means uniformly found in cases of mercuric chlorid poisoning, and even some of the more severe cases have shown albumin only for comparatively short periods.

Most of the other patients included in this series left the hospital recovered or in such condition that recovery seemed assured, and careful search of records of the coroner's office shows no report of deaths other than those here recorded

### ILLUSTRATIVE CASES

The following cases present features of special interest and are therefore presented in greater detail than the previous tables permit

CASE 1—Margaret I (No 766586), aged 40, weight approximately 135 pounds (61.2 kg), was admitted to the hospital on July 16, 1921, at 10 p m, with a history of having taken eleven tablets of mercuric chlorid (probably 20.02 grains) twenty-eight hours previously. The patient had vomited repeatedly and was having frequent involuntary defecations. Examination of the stomach washings on admission showed considerable quantities of mercury, and mercury continued to be present in every specimen of stomach washings up to and including the eleventh day. The patient was catheterized repeatedly, and no urine was obtained until the fourth day in the hospital when 10 cc were obtained, as shown in the accompanying table. She reported that she passed small amounts of urine at the time of bowel movements during the next few days, but although she was catheterized no further urine was obtained for examination, until the tenth day.

TABLE 3—*Blood Chemistry in Case 1*

	Day				
	Second	Fourth	Sixth	Eleventh	Fourteenth
Urea nitrogen	33.62	53.70	73.60	92.00	116.00
Urea	71.94	113.42	157.50	196.80	248.20
Uric acid	4.16	4.21	6.21	8.27	8.93
Creatinin	4.27	6.11	8.87	10.19	11.37

TABLE 4—*Urine Examinations in Case 1*

Day	Amount	How Obtained	Color	Reaction	Albumin	Sugar	Blood	Pus	Casts
2	0	Catheterization							
4	10 cc	Catheterization	Straw	Acid		0	0		0
6	Trace	Lost with stool account of diarrhea			No specimen obtainable				
7	Trace	Lost with stool account of diarrhea							
8	Trace	Lost with stool account of diarrhea							
9	0	Catheterization							
10	15 cc?	Spontaneously	Straw	Acid		0	0		Occasional hyaline
13		Lost with stool							

Rosenbloom treatment as previously outlined was instituted immediately on admission to the hospital. So far as could be ascertained, no treatment had been instituted prior to the patient's admission to the hospital. This patient, therefore, presents a longer interval before treatment than any of the other cases in the series, and though the dose of poison taken was much less than that from which other patients in the series recovered, the patient died on July 29, 1921, thirteen days after admission.

as in the other kidney lesions in which they have been most studied. Low grade nitrogen retention bespeaks recovery, but high figures do not necessarily mean a fatal termination (see C M ). The value of the creatinin test, which has been particularly advocated, as a prognostic sign is much greater in chronic kidney disease than in acute conditions comparable to the one herein observed. This is in agreement with the previous report of Campbell.



TABLE 7—*Blood Chemistry*

Day	Urea Nitrogen	Urea	Creatinin
2	19.61	41.96	1.51
6	13.07	27.96	

TABLE 8—*Urine Examinations*

Day	Appearance	Specific Gravity	Reaction	Albumin	Sugar	Leukocytosis	Casts
1	Clear	1.020	Alkaline	++	0	Few	Many granular
3	Cloudy	1.028	Acid	+++	0	++	Many granular
4	Cloudy	1.010	Alkaline	++	0	++	Few granular
5	Cloudy		Alkaline	+	0	++	Few granular

## DISCUSSION

For a long time there has apparently been a general impression both among the laity and in medical literature that mercuric chlorid poisoning is almost uniformly fatal. This view has been strengthened by the researches of Meyer and Gottlieb, and of Sansum, particularly by the work of the latter concerning the uniformity of the minimum lethal dose when mercuric chlorid is given intravenously to dogs. Conditions for absorption of this poison when taken by mouth, however, are quite different from those observed experimentally, and from our observations it is quite evident that patients in whom the prognosis *a priori* appears bad, either because of large dose or late treatment, may recover. It is therefore essential that all patients be treated carefully even though conditions appear most unfavorable for recovery—as, for example, in the case of C. M. with prolonged anuria, high nitrogen retention, etc.

The aim of therapy is to block every possible avenue of absorption and to remove from the body as much mercury as possible. In our experience this has seemed to be best accomplished with the method of Rosenbloom. It is especially interesting to note the long period in which we have continued to obtain mercury in stomach washings. It is to be regretted that we have been unable to obtain quantitative analyses of the mercury thus removed. It would seem that in many cases the amount is considerable and that it might readily, in some cases at least, make the difference between a lethal and nonlethal dose. It seems quite essential that the washings should be tested for mercury and the treatment continued until it is quite certain that no further mercury will be removed in this way.

Blood chemistry determinations have furnished much interesting data and would seem to be of some value in prognosis. These figures, however, do not have in mercuric chlorid poisoning the same significance

neurosyphilitic persons than among those married to patients with diffuse cerebrospinal (meningovascular) neurosyphilis<sup>2</sup> This fact, together with other differences between the two groups, led us to suggest the possibility of the existence of two neurotropic strains of the organism, the lesions caused by one of these being largely confined to the nervous system (parenchymatous type)

The practical and probable scientific value of the study has led us to continue the work during the past two years. An additional sixty-one families have now been studied from this point of view, making a total of 111 families at our disposal. In this paper will be reported the details of the recent sixty-one families, together with a summary of the whole series. The unselected character of the material is emphasized, as each neurosyphilitic patient enters the clinic he is urged to bring his spouse in for examination. Only those marital partners in whom are obtainable anamnesis, physical and neurologic examination, blood Wassermann tests, and spinal fluid study are included, the absence of any one of these rendering the case too incomplete for consideration. These data are also available in the original patient.

Of the sixty-one new families, the original member (not always the one to acquire syphilis and introduce it into the family) was paretic in fourteen instances, tabetic in seventeen, and in thirty instances had cerebrospinal syphilis (early or late). The material will be considered under these headings.

#### GENERAL PARALYSIS

In Table 1 are summed up the details of the examination of the marital partners of fourteen paretic patients. Six of these were apparently normal, eight, or 57.1 per cent, were syphilitic. Of these, three were neurosyphilitic, in two instances (and probably the third) the neurosyphilis being of the parenchymatous type. Clinical neurosyphilis was also present in the wives of two other paretic men, the families not being included in the tables because of the lack of spinal fluid examinations. In Family 74, neurosyphilis was detected only by the routine use of spinal puncture.

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<sup>2</sup> In this paper the term parenchymatous neurosyphilis includes general paresis, tabes dorsalis, and taboparesis. Other neurosyphilitic diseases are classified under the general heading of cerebrospinal syphilis, the descriptive terms meningeal, vascular, meningovascular, neurorecurrence, asymptomatic, etc., being used when possible. In many cases the neurologic abnormalities will not permit accurate localization of the lesions; these cases in our nomenclature, are referred to as syphilis C N S unclassified, or diffuse cerebrospinal syphilis.

# STUDIES IN FAMILIAL NEUROSYPHILIS

## III CONJUGAL NEUROSYPHILIS (SECOND COMMUNICATION)\*

JOSEPH EARLE MOORE, MD

AND

JAROLD E KEMP, MD

BALTIMORE

In the first paper of this series<sup>1</sup> we outlined the methods employed in and reported the results of the examinations of fifty-two marital partners of fifty neurosyphilitic persons, with the thought that the data thus obtained might be of value in the debate as to the existence of a neurotropic strain of *Spnochaeta pallida*. It was recognized that the family material employed in such a study must be as nearly as possible unselected and that the methods of examination must include not only the usual Wassermann survey, or physical and neurologic examination, but also, in view of our increasing knowledge of asymptomatic neurosyphilis, all these procedures plus routine examination of the cerebrospinal fluid of every available marital partner of a series of neurosyphilitic patients. The value of this method of approach was indicated by the discovery of asymptomatic neurosyphilis in seven marital partners, the abnormal spinal fluid findings being the sole indication of syphilis in three of these.

Although the literature contained many reports of series of families with conjugal neurosyphilis and a few excellent studies of routine physical or Wassermann examinations of the marital partners of neurosyphilitic persons, we were unable to find any communications in which the data given were strictly comparable to our own, and since the date of our publication (July, 1921) no further satisfactory studies have appeared.

Owing to the comparatively small number of families reported in our first paper, no definite conclusions as to the duality of strain of *Spnochaeta pallida* were permissible. It did appear, however, that conjugal neurosyphilis was of relatively frequent occurrence. It was noted to be more common among the partners of parenchymatous

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\* From the Syphilis Department of the Medical Clinic, Johns Hopkins Hospital.

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1 Moore, J. E., and Keidel, A. Studies in Familial Neurosyphilis. I. Conjugal Neurosyphilis, J. A. M. A. **77** 1 (July 2) 1921.

A comparison of these families with the twenty-one families discussed in our earlier paper appears in Table 2. The data show discrepancies, probably explainable on the basis of the small number of families in each group. In the total, thirty-five families, one third of the partners were normal, two thirds were syphilitic, and of the syphilitic partners, 58.3 per cent had neurosyphilis. In the fourteen partners with neurosyphilis, the type of the disease was certainly or probably parenchymatous (as in the original patient) in eleven instances.

## TABLES

The seventeen new families of tabetic patients are shown in Table 3. Nine of the marital partners were normal, eight, or about one half, had syphilis. Of the latter, four, or 50 per cent, were neurosyphilitic. Here, however, the type of neurosyphilis was the same as in the person who introduced syphilis into the family in only one instance (Family 103).

TABLE 2—*Summary of Families with General Paresis*

	Number of Families	Number of Partners Investigated	Number of Partners Normal	Total Number of Partners Syphilitic	Per- centage of Partners Syphilitic	Partners Probably or Certainly Neuro- syphilitic	Per centage of Syphilitic Partners with Neuro syphilis
Moore and Keidel	21	22	6	16	72.7	11	68.7
This study	14	14	6	8	57.1	3	37.5
Total	35	36	12	24	66.6	14	58.3

A comparison of the whole number of tabetic families, shown in Table 4, with the series of paretic families in Table 2, shows striking similarities. The incidence of syphilis in the partners of the two groups is about the same, and the incidence of neurosyphilis among the syphilitic partners almost precisely so. More than half of the syphilitic marital partners of patients with parenchymatous neurosyphilis were themselves neurosyphilitic.

## CEREBROSPINAL SYPHILIS GROUP

This group of patients, which in our first communication was considered as a whole, has here been split into two parts to facilitate discussion. The first subgroup includes those families in which one member was found to be neurosyphilitic, either by clinical evidence or by routine spinal puncture, within the first eighteen months of his infection. The second is made up from families in which the original member, having had syphilis for some years, was found to have clinical cerebrospinal syphilis of various types on admission. The tables and

TABLE 1—Group of Families with General Paresis

Family Number	Person Introducing Syphilis	Diagnosis in Person Introducing Syphilis	Duration of Syphilis, Years	Duration of Marriage, Years	History of Syphilis	Condition of Partner (Wife or Husband)						Diagnosis in Partner
						Physical Examination	Blood Wassermann Test	Cerebrospinal Fluid				
								Cells	Globulin	Wassermann Test	Colloidal Tests	
72	Husband	General paralysis	12	8	None	Negative	0	3	0	0	Negative	Nonsyphilitic
73	Husband	General paralysis	?	12	Three miscarriages	Gumma of tongue, neurologic examination negative	4	3	0	0	Negative	Tertiary syphilis
74	Husband	General paralysis	?	6	None	Negative	1	?	+++	4	Paretic	Cerebrospinal syphilis, asymptomatic
75	Husband	General paralysis	?	6	Indefinite history of rash	Negative	0	0	0	0	Negative	Nonsyphilitic
76	Husband	General paralysis	?	4	None	Negative	1	2	0	0	Negative	Syphilis (Wassermann)
77	Husband	General paralysis	20	13	None	Unequal, irregular pupils	1	1	0	0	Negative	Syphilis (Wassermann)
78	Husband	General paralysis	?	17	Rash 3 months after marriage	Pupils sluggish to light	4	0	0	0	Negative	Syphilis (Wassermann)
79	Husband	General paralysis	5	20	None	Negative	0	0	0	0	Negative	Nonsyphilitic
80	Husband	General paralysis	12	1½	Vague history of rash	Negative	4	2	0	0	Negative	Syphilis (Wassermann)
81	Husband	General paralysis	?	5	None	Negative	0	?	0	0	Negative	Nonsyphilitic
82	Wife	General paralysis	?	16	None	Negative	0	0	0	0	Negative	Nonsyphilitic
85	Husband	General paralysis	?	5	None	Unequal, sluggish pupils, knee jerks and ankle reflexes absent, Romberg sign +	0	1	0	0	Negative	Cerebrospinal syphilis, tabes
86	Husband	General paralysis	?	14	Rash and alopecia shortly after marriage	Irregular pupils, Romberg +, speech and memory defect	4	3	+	4	Paretic	Cerebrospinal syphilis, general paresis
87	Husband	General paralysis	20	10	None	Negative	0	3	0	0	Negative	Nonsyphilitic

descriptions include twenty-one families from our first communication and thirty additional families, the earlier data being purposely repeated because of the regrouping

#### EARLY CEREBROSPINAL SYPHILIS

Included in this group, details of which are shown in Table 5, are five families from our first paper (Families 17, 28, 12, 45 and 52) and thirteen additional families. Particular interest attaches to this group, since the entrance of syphilis into the family is recent, the duration of infection in husband and wife approximately the same, and since in one member early invasion of the nervous system by the organism had been detected. As may be seen from a study of the table, in each instance the one who introduced syphilis had recently contracted the disease and was usually first seen with the lesions of primary or secondary syphilis. The average duration of infection in the original patient was five and nine-tenths months. In these families, it is certain that the strain of organism infecting husband and wife is

TABLE 4—*Summary of Families with Tables*

	Number of Families	Number of Partners Investigated	Number of Partners Normal	Total Number of Partners Syphilitic	Per centage of Partners Syphilitic	Partners Probably or Certainly Neuro- syphilitic	Per- centage of Syphilitic Partners with Neuro- syphilis
Moore and Keidel	8	8	2	6	75.0	4	66.6
This study	17	17	9	8	47.0	4	50.0
Total	25	25	11	14	57.1	8	57.1

the same. If the fact of early nervous system invasion in one member be considered as evidence of neurotropism of the spirochete, neurosyphilis ought to be frequent among the marital partners. This statement, of course, disregards other factors, such as the kind and amount of early treatment, the patients' immune processes, etc., which may, and certainly do, influence the outcome. Contrary to expectation, however, neurosyphilis in the marital partners of this group is uncommon.

Of the eighteen partners, only three were normal. As the one introducing syphilis had recently had infectious lesions, fifteen were syphilitic, all of whom had acquired the disease but a short time before examination. In fourteen of the eighteen families, the member with the original infection was neurosyphilitic, the neurosyphilis being asymptomatic eight times, of the neurorecurrence type four times, and clinical neurosyphilis (without previous insufficient treatment) twice. Eleven of the fourteen partners of these patients had syphilis, of whom, however, only three were neurosyphilitic.

In Family 12, the one who introduced syphilis developed an eighth nerve neurorecurrence after insufficient treatment, his wife, with no

TABLE 3—Group of Families with Tabes

Family Number	Person introducing Syphilis	Diagnosis in Person Introducing Syphilis	Duration of Syphilis, Months	Duration of Marriage, Years	Condition of Partner (Wife or Husband)					Diagnosis in Partner	
					History of Syphilis	Physical Examination	Blood Wassermann Test	Cerebrospinal Fluid			
								Cells	Globulin		Wassermann Test
88	Husband	Tabes	6	?	None	Negative	0	2	0	0	Nonsyphilitic
89	Husband	Tabes	14	32	None	Unequal irregular pupils, reflexes hyperactive	0	3	+	0	Cerebrospinal syphilis undoubted (?)
90	Husband	Tabes	?	18	None	Negative	0	2	0	0	Nonsyphilitic
91	Husband	Tabes	20	18	None	Irregular pupils, otherwise normal	+	?	0	?	Syphilis (Wassermann undoubted)
92	Husband	Tabes	26	17	None	Negative	0	1	0	0	Nonsyphilitic
93	Husband	Tabes	?	?	Vague	Negative	0	2	0	0	Nonsyphilitic
94	Husband	Tabes	17	7	None	Gumma soft palate	+	0	0	0	Tertiary syphilis
95	Wife	Tabes	?	10	Primary 8 years ago	Unequal irregular pupils	+	10	++	+	Cerebrospinal syphilis, undoubted
96	Husband	Tabes	?	?	None	Negative	0	0	0	0	Nonsyphilitic
97	Husband	Tabes	?	25	None	Negative	0	0	0	0	Nonsyphilitic
98	Husband	Tabes	10	5	None	Negative	0	0	0	0	Nonsyphilitic
99	Husband	Tabes	20	16	His borne a child with congenital syphilis	Negative	0	0	0	0	Syphilis histologic
102	Husband	Tabes	?	22	None	Negative	0	0	0	0	Nonsyphilitic
103	Husband	Tabes	16	14	None	Optic atrophy	+	7	+	+	Cerebrospinal syphilis, undoubted
105	Husband	Tabes	34	33	None	Irregular pupils hyperactive	+	?	++	+	Cerebrospinal syphilis, undoubted
106	Wife	Tabes	?	14	None	Negative	0	0	0	0	Nonsyphilitic
123	Wife	Tabes	?	15	None	Slight difference in deep reflexes	+	4	0	0	Syphilis (Wassermann undoubted)

history of early syphilis or treatment, at the same time had a right facial paralysis of one week's duration and a positive cerebrospinal fluid. In Family 52, husband and wife, both with early syphilis, were discovered to have spinal fluid abnormalities of the same type (Group 2 of our classification of early asymptomatic neurosyphilis).<sup>3</sup> The husband in Family 116 showed definite clinical evidence of neurosyphilis and a positive spinal fluid on admission, his wife developed a neuro-recurrence involving the optic nerve after insufficient treatment.

In the last four families of the table (118, 119, 107 and 120), the one who introduced syphilis was normal from the neurologic standpoint, while his marital partner whom he had infected developed asymptomatic neurosyphilis. It is of particular interest that the husbands in Families 118 and 119 were infected by the same prostitute, neither of them developed neurosyphilis, but in both families the wives had positive spinal fluids without clinical signs.

#### LATE CEREBROSPINAL SYPHILIS

In Table 6 appear the data regarding this group of families, sixteen of which are transferred from our first paper (No. 51 and below), while seventeen are new. Of the thirty-four marital partners of thirty-three neurosyphilitic persons, nine were normal and twenty-five, or 73.5 per cent, were syphilitic. Seven of the syphilitic partners, or 28 per cent, had neurosyphilis. In four families (71, 60, 67 and 62), the one introducing syphilis did not show any evidence of nervous system damage, although the infected partner was neurosyphilitic. The type of neurosyphilis in the partner was roughly similar to that in the original patient in two families, dissimilar in one, and asymptomatic in the remaining four.

A summary of the families with early and late cerebrospinal syphilis is given in Table 7. Striking differences from the parenchymatous group, both as to the incidence of syphilis and of neurosyphilis in the partners, are evident. Further attention will be directed to this point.

#### TYPES OF CONJUGAL NEUROSYPHILIS IN MARITAL PARTNERS

The value of routine spinal puncture in this type of study is admirably shown by the data summed up in Table 8. Of thirty-two cases of neurosyphilis in marital partners, no less than nine, or 26.1 per cent, would have been overlooked had not this procedure been employed. It is further evident that conjugal neurosyphilis of the same general clinical type is fairly common. The asymptomatic part-

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<sup>3</sup> Moore, J. E. Studies in Asymptomatic Neurosyphilis. II. The Classification, Treatment, and Prognosis of Early Asymptomatic Neurosyphilis, *Bull. Johns Hopkins Hosp.* **33**: 231, 1922.



TABLE 5—Group of Families with Early Cerebrospinal Syphilis (Syphilis of Less Than Eighteen Months' Duration in Family)

Family Number	Person Introducing Syphilis	Diagnosis in Person Introducing Syphilis	Duration of Syphilis, Months	Duration of Marriage, Years	History of Syphilis	Condition of Partner (Wife or Husband)					Diagnosis in Partner	
						Physical Examination	Blood Wassermann Test	Cerebrospinal Fluid				
								Cells	Globulin	Wassermann Test		Colloidal Tests
17	Wife	Cerebrospinal syphilis, asymptomatic	12	13	Infected 5 months before wife, whose spinal fluid was found routinely positive	Recurrent secondary rash no neurologic signs	4	2	0	0	Negative	Recurrent secondary syphilis
28	Husband	Cerebrospinal syphilis, asymptomatic	4	2	Developed secondary syphilis concurrently with husband	Maculopapular rash, palmar syphilitic, no neurologic signs	4	0	0	0	Negative	Early secondary syphilis
12	Husband	Neurorecurrence, left neuroretinitis, bilateral eighth nerve	15	1	None	Right facial paralysis, 1 week	4	18	++	4	Syphilitic zone	Meningeal neurosyphilis
45	Husband	Cerebrospinal syphilis, meningeal	?	6	Five years after marriage, secondary syphilis	Negative except for signs of secondary syphilis	4	2	0	0	Negative	Early secondary syphilis
52	Wife	Cerebrospinal syphilis, asymptomatic	?	½	Four months ago primary, followed by secondary lesions	Lesions of secondary syphilis, no neurologic signs	4	16	+	0	Syphilitic zone	Secondary syphilis and asymptomatic cerebrospinal syphilis
108	Husband	Primary, cerebrospinal syphilis, asymptomatic	1¼	13	None	Negative	0	0	0	0	Negative	Nonsyphilitic
109	Husband	Secondary, cerebrospinal syphilis, asymptomatic	6	1	General sore 5 months ago	Negative	4	0	0	0	Negative	Syphilis, Wassermann (early)
110	Wife	Secondary, cerebrospinal syphilis, asymptomatic	2	1½	None	Negative	0	0	0	0	Negative	Nonsyphilitic
111	Wife	Secondary, cerebrospinal syphilis, asymptomatic	6	1½	None	Macular syphilitic	4	0	0	0	Negative	Early secondary syphilis
112	Husband	Secondary, cerebrospinal syphilis, asymptomatic	5	3	None	Negative	0	0	0	0	Negative	Nonsyphilitic
113	Husband	Acute syphilitic meningitis	6	5	Genital sore for 1 month	Roseola	4	0	0	0	Negative	Early secondary syphilis
114	Husband	Cerebrospinal syphilis, unclassified	8	2	Genital sore 6 months ago	Annular syphilitic	4	0	0	0	Negative	Early secondary syphilis
115	Husband	Neurorecurrence, second and eighth nerves	7	3	Rash for 10 days	Pustular syphilitic	4	0	0	0	Negative	Early secondary syphilis
116	Husband	Cerebrospinal syphilis, unclassified	12	½	None	Wassermann test positive on admission, developed a neurorecurrence after lapse in treatment	4	0	0	0	Negative	Cerebrospinal syphilis, neuroretinitis
118*	Husband	Primary syphilis, cerebrospinal fluid negative	1	6	None	Pupils sluggish	4	?	+	4	Paretic	Asymptomatic cerebrospinal syphilis
119*	Husband	Secondary syphilis, cerebrospinal fluid negative	2	2	None	Negative	4	0	+	4	Paretic	Asymptomatic cerebrospinal syphilis
107	Husband	Primary syphilis, cerebrospinal fluid negative	2	1	Rash for 2 months	Secondary syphilis, lapse after insufficient treatment neurorecurrence, bilateral eighth nerve involvement	4	1	+	4	Paretic	Cerebrospinal syphilis, neurorecurrence
120	Wife	Syphilis Wassermann, cerebrospinal fluid negative	?	½	None	Mucous patches in throat unequal irregular slugs fish pupils	4	0	+	0	Paretic	Asymptomatic cerebrospinal syphilis

11	Wife	Cerebrospinal syphilis, asymptomatic	5	Infected 2 years before wife, whose spinal puncture was routine diagnostic measure	Negative	4	6	0	0	Negative	Syphilis (Wassermann)
27	Husband	Cerebrospinal syphilis, meningeal	24	Shortly after marriage sore throat, bone pains, malaise lasting 6 months	Pupils irregular, sluggish, reflexes exaggerated	0	3	0	0	Negative	Nonsyphilitic (?)
51	Husband	Cerebrospinal syphilis, meningeal	5	Negative, has had a syphilitic child	Negative	1	0	0	0	Negative	Latent syphilis
53	Husband	Cerebrospinal syphilis, unclassified	?	Rash 1 year ago	Inequalities of deep reflexes	4	?	+	4	Paretic	Cerebrospinal syphilis, unclassified
54	Husband	Cerebrospinal syphilis, unclassified	?	None	Negative	4	0	0	0	Negative	Syphilis (Wassermann)
57	Wife	Cerebrospinal syphilis, unclassified	24	None	Negative	6	0	0	0	Negative	Nonsyphilitic
58	Husband	Cerebrospinal syphilis, unclassified	?	None of early syphilis	Skin gumma, neurologic examination negative	4	0	0	0	Negative	Tertiary syphilis
59	Wife	Cerebrospinal syphilis, unclassified	6	None	Roseola	4	0	0	0	Negative	Early secondary syphilis
61	Husband	Cerebrospinal syphilis, unclassified	17	None	Negative	4	0	0	0	Negative	Syphilis (Wassermann)
56	Husband	Cerebrospinal syphilis, meningeal	?	None	Negative	0	0	0	0	Negative	Nonsyphilitic
68	Husband	Cerebrospinal syphilis, optic atrophy	?	None	Reflexes hyperactive	0	19	+++	4	Paretic	Asymptomatic cerebrospinal syphilis
55	Husband	Cerebrospinal syphilis, optic atrophy	?	None of early syphilis	Gumma soft palate, neurologic examination negative	4	2	+	4	Paretic	Tertiary and cerebrospinal syphilis, asymptomatic
69	Husband	Cerebrospinal syphilis, meningovascular	12	None	Negative	0	0	0	0	Negative	Nonsyphilitic
70	Husband	Cerebrospinal syphilis, unclassified	3	Two spontaneous abortions	Negative	0	0	0	0	Negative	Nonsyphilitic (?)
71	Husband	Tertiary syphilis, cerebrospinal fluid	12	None	Irregular, sluggish pupils	4	4	+	4	Paretic	Cerebrospinal syphilis, unclassified
60	Husband	Syphilis Wassermann, cerebrospinal fluid	7	None	Roseola, neurologic examination negative	4	7	+	1	Paretic	Secondary and cerebrospinal syphilis, asymptomatic
67	Husband	Syphilis Wassermann, cerebrospinal fluid	5	None	Roseola, neurologic examination negative	4	8	++	0	Paretic	Secondary and cerebrospinal syphilis, asymptomatic
62	Husband	Syphilis Wassermann, cerebrospinal fluid	15	None	Irregular pupils, reflexes hyperactive	4	?	++	4	Paretic	Cerebrospinal syphilis, unclassified
121	Husband	Cerebrospinal syphilis, vascular	4	Rash for 2 months	Maculopapular syphilid, irregular sluggish pupils	4	3	0	0	Negative	Early secondary syphilis
122	Husband	Cerebrospinal syphilis, unclassified	?	Rash for 6 weeks	Maculopapular syphilid	4	?	0	0	Negative	Early secondary syphilis

TABLE 6—Group of Families with Late Cerebrospinal Syphilis (Duration of Disease in Family More Than Two Years)

Family Number	Person introducing Syphilis	Diagnosis in Person Introducing Syphilis	Duration of Syphilis, Years	Duration of Marriage, Years	History of Syphilis	Condition of Partner (Wife or Husband)					Diagnosis in Partner	
						Physical Examination	Blood Wassermann Test	Cerebrospinal Fluid				
								Cells	Globulin	Wassermann Test		Colloidal Tests
1	Husband	Vascular epilepsy	?	3½	Late secondary rash 6 months after husband's nervous symptoms	Negative	+	3	0	0	Negative	Syphilis (Wassermann)
6	Husband	Vascular hemiparesis	2	2	Primary syphilis 2 months after husband's primary	Mydrasis, otherwise negative	0	8	0	0	Negative	Latent syphilis
25	Husband	Vascular hemiparesis	14	16	Negative	Anisocoria, sluggish pupils, auditory hallucinations	+	112	+++	4	Paretic	General paresis
36	Husband	Vascular hemiparesis	4	2	Negative	Negative	+	2	0	0	Negative	Syphilis (Wassermann)
2	Husband	Cerebrospinal syphilis, unclassified	6	8	Negative	Negative	0	0	0	0	Negative	Nonsyphilitic
3	Husband	Cerebrospinal syphilis, unclassified	4	15	Secondary rash after husband's infection	Negative	+	0	0	0	Negative	Syphilis (Wassermann)
4	Husband	Cerebrospinal syphilis, unclassified	9	6	Negative	Negative	0	0	0	0	Negative	Nonsyphilitic
14	Husband	Cerebrospinal syphilis, unclassified	4	3	Doubtful history of rash	Negative	+	27	+++	4	Paretic	Asymptomatic neurosyphilis
19	Husband	Cerebrospinal syphilis, unclassified	?	7	(A) Wife none of early syphilis, gumma of soft palate (b) Mistress negative	Negative, except for tertiary lesion	0	0	±	0	Negative	Tertiary syphilis
31	Husband	Cerebrospinal syphilis, unclassified	14	13	Negative	Negative	0	0	0	0	Negative	Nonsyphilitic
37	Husband	Cerebrospinal syphilis, unclassified	27	7	Just after marriage, rash lasting 4 weeks, for 2 years headache, girdle sensation	Negative, except for hyperextension, eccentric irregular pupils, reflexes hyperactive	0	1	±	0	Negative	Nonsyphilitic
39	Husband	Cerebrospinal syphilis, unclassified	6?	3	Alopecia 5 months before, congenital syphilitic child	Negative	0	63	+++	4	Paretic	Asymptomatic neurosyphilis
41	Husband	Cerebrospinal syphilis, unclassified	9	7	Extragenital (lip) 2 years ago well treated	Negative for neurologic signs	0	5	0	0	Negative	Primary syphilis treated

is that a neurosyphilitic person may be infectious over long periods of time, since of eleven of such patients infected more than five years before marriage, four transmitted the disease to their spouses. Three of these were paretic or tabetic, demonstrating that in these instances, at least, the invading organism had attacked not only the central nervous system, but was also capable of producing lesions elsewhere (skin, mucosa, or testis), thus providing for egress of the organism from the host and propagation of the strain. These instances meet the objection raised by the antagonists of neurotropism, namely, that a strain of organism invading chiefly the nervous system must soon disappear because of its inability to reach the exterior and reproduce itself. It is obvious that in many patients with parenchymatous neurosyphilis other organs than the nervous system may be, and sometimes are, involved.

TABLE 9—*Duration of Syphilis in Originally Infected Partner in Relation to Time of Marriage and Status of Health of Spouse*

Duration of Syphilis in One Introducing Syphilis More than 10 years before marriage From 5 to 10 years before From 1 to 5 years before Year of marriage After marriage Duration unknown	Status of Wife or Husband								
	Parenchymatous Group			Group with Late Cerebrospinal Syphilis			Total		
	Normal	Syphilitic	Percentage Syphilitic	Normal	Syphilitic	Percentage Syphilitic	Normal	Syphilitic	Percentage Syphilitic
One Introducing Syphilis More than 10 years before marriage	3	2	40.0	1	1	50.0	4	3	42.8
From 5 to 10 years before	3	1	25.0				3	1	33.3
From 1 to 5 years before	6	8	57.1	2	7	77.7	8	15	65.2
Year of marriage		3	100.0	2	2	50.0	2	5	71.4
After marriage	1	5	83.3	2	7	77.7	3	12	80.0
Duration unknown	11	17	62.9	2	8	80.0	13	25	65.7

The average duration of syphilis in the original patient of the paretic group was 16.6 years, in the tabetic, 17.2 years (combined average for the parenchymatous group, 16.9 years), in the late cerebrospinal group, on the contrary, it was 10.6 years. This indicates that in general neurologic symptoms appear some years earlier in diffuse than in parenchymatous neurosyphilis.<sup>4</sup> It also raises the question, however, as to how many of the patients whose disease was diagnosed as cerebrospinal syphilis on admission would have developed tabes or paresis if allowed to go untreated. If the transition from one group to the other is common, our conclusions as to the varying incidence of conjugal neurosyphilis in the two groups are probably at fault. This point cannot be answered definitely, we can only say that in our experience such a transition in the type of neurosyphilitic disease is uncommon.

<sup>4</sup> Fournier, A. *Traitement de la syphilis*, Paris, Vigot Freres, 1909, p. 442. Fournier has made almost precisely the same observation.

ners of the parenchymatous group all showed spinal fluids of our Group 3 type (abnormalities usually present in paretic fluids) <sup>3</sup> and are probably to be regarded as candidates for future parenchymatous neurosyphilis. In general, furthermore, the asymptomatic partners of the patients with cerebrospinal syphilis would be classed in our Group 2,<sup>3</sup> which we regard as the serologic precursor of clinical diffuse cerebrospinal syphilis. If these predictions as to future course are correct, then conjugal neurosyphilis of the same type is even more frequent than is indicated by the table. The material is too small to permit any comparisons between the parenchymatous and cerebrospinal groups, although it is our impression, unfortified by figures, that

TABLE 7—*Summary of Families with Cerebrospinal Syphilis*

	Number of Families	Number of Partners Examined	Number of Partners Normal	Total Number of Partners Syphilitic	Percentage of Partners Syphilitic	Partners Probably or Certainly Neuro Syphilitic	Percentage of Syphilitic Partners with Neuro syphilis
Early cerebrospinal syphilis	18	18	3	15	83.6	3	20.0
Late cerebrospinal syphilis	33	34	9	25	73.5	7	28.0
Total	51	52	12	40	76.5	10	25.0

TABLE 8—*Types of Conjugal Neurosyphilis Observed in 111 Families*

Neurosyphilitic Disease in Person Introducing Syphilis	Number of Instances of Conjugal Neuro syphilis	Type of Neurosyphilis in Partner Probably Similar to That in the One Introduced during Syphilis	Neuro syphilis in Partner Dissimilar in Type	Neuro Syphilis in Partner Asymptomatic
Parenchymatous ( paresis or tabes )	22	8	9	5
Cerebrospinal (early or late)	10	4	2	4

parenchymatous neurosyphilis is more common among the partners of paretic and tabetic persons than among those of persons with cerebrospinal syphilis.

#### RELATION OF SYPHILIS IN MARITAL PARTNER TO TIME OF MARRIAGE AND DURATION OF INFECTION IN ORIGINAL PARTNER

The data relating to these points are summed up in Table 9. As in our first paper, it is shown that the danger of infection for the partner increases as the date of infection in the one introducing syphilis approaches the year of marriage. The group of families with early cerebrospinal syphilis is purposely omitted, since here recent infection was common in both the person acquiring syphilis and in the marital partner. A point of considerable interest appearing from this material

four women, the male, as usual, being the member to introduce syphilis into the family. The small number of male partners precludes any accurate comparison. The data as to the females, however, are shown in Table 11.

In about 2,500 syphilitic women, whites and negroes, representing all stages of the disease, the incidence of all types of clinical neurosyphilis is 6.47 per cent. As is shown by the table, an additional 18.2 per cent of women (with early and late syphilis) without definite neurologic signs present definite abnormalities in the cerebrospinal fluid. It may be fairly stated, therefore, that in a large unselected group of women with syphilis, the incidence of neurosyphilis, clinical or asymptomatic, is approximately 25 per cent.

The incidence of neurosyphilis among the wives of men with parenchymatous neurosyphilis is more than twice as great as in the

TABLE 11—*Actual Incidence of Neurosyphilis Among Wives of Neurosyphilitic Men, Compared with Expected Incidence in an Unselected Group of Women*

Group		Total Number of Women	Number of Women Syphilitic	Number of Women Neuro syphilitic	Percentage Incidence of Neuro syphills
Partners of	parenchymatous neurosyphilitic persons	52	33	19	57.5
Partners of	cerebrospinal syphilitic persons	12	32	9	28.1
Unselected Group of Female Syphilitics	Clinical neurosyphilis		2438	158	6.47
	Asymptomatic neurosyphilis	{	Early syphilis	113	22.1
			Late syphilis	233	16.3
	Total				

unselected group. In the wives of men with cerebrospinal neurosyphilis it is only half that of the parenchymatous group and only slightly greater than in the unselected series. A study of these figures renders it difficult to escape the conclusion that there is a neurotropic strain of *Spinochaeta pallida*, which has a special predilection for nervous tissue, and that this strain of organism tends especially to cause parenchymatous neurosyphilis.

It has been apparent throughout this paper that marked differences exist between the parenchymatous and the cerebrospinal groups. In order to determine whether these differences are found only in our own material or in that of other investigators as well, we have compared our data with those of Plaut and Goring,<sup>7</sup> Schacherl,<sup>8</sup> Raven,<sup>9</sup> and

7 Plaut, F., and Goring, M. H. Untersuchungen an Kindern und Ehegatten von Paralytikern, München med. Wchnschr. **58** 1959, 1911.

8 Schacherl, M. Ueber Luetikerfamilien, Jahr f. Psychiat. u. Neurol. **36** 521, 1914.

9 Raven, W. Serologische und klinische Untersuchungen bei Syphilitiker-familien, Deutsch. Ztschr. f. Nervenh. **51** 342, 1914.

LESIONS OF EARLY SYPHILIS IN THE MARITAL PARTNERS OF  
PERSONS WITH NEUROSYPHILIS

Prominent among others, Fournier <sup>5</sup> has called attention to the fact that in neurosyphilitic persons, particularly in paretic patients, early lesions of syphilis are often conspicuous by their absence. In our first paper <sup>1</sup> attention was drawn to this point in the partners of neurosyphilitic persons. Complete latency of infection was the rule among the syphilitic partners of parenchymatous neurosyphilitic patients, while of the spouses of patients with cerebrospinal syphilis, two thirds had shown manifestations of the disease outside the nervous system. The material provided by our total, 111 families, summed up in Table 10, shows this striking discrepancy. Of the syphilitic partners of persons with parenchymatous neurosyphilis, less than one third had had obvious lesions of the disease, while among the partners of persons with cerebrospinal syphilis, more than two thirds had had definite

TABLE 10—*Lesions of Syphilis Other Than Neurosyphilis in Marital Partners of Neurosyphilitic Persons*

Type of Neurosyphilitic Disease in Person Introducing Syphilis	Total Number of Partners Syphilitic	History or Lesions of Syphilis in Partners		Complete Latency of Infection (Except for Neurosyphilis)	Percentage of Syphilitic Partners with Lesions	Percentage of Partners Showing Complete Latency
		Early (Primary or Secondary)	Late (Tertiary)			
Parenchymatous	38	9	3	26	31.5	68.5
Early cerebrospinal	15	11		4	73.4	26.6
Late cerebrospinal	26	15	3	8	69.3	30.7

early lesions. This difference in the general course of syphilis, together with the other points of variance already mentioned, suggests a quite different pathogenesis for the two main types of neurosyphilitic disease, either due to difference in strain of organism or to similar differences in the defense mechanism of groups of persons.

COMMENT

It is not permissible to draw conclusions as to the probable frequency of conjugal neurosyphilis until a comparison has been instituted between the percentage of incidence of neurosyphilis in the partners of neurosyphilitic persons and in an unselected class of syphilitic patients whose disease is approximately of the same duration. Fortunately, an accurate comparison may be made with unselected material from our own clinic, the details of which have been reported in previous papers <sup>6</sup>. Of the total 113 partners of our 111 families, nineteen were men and ninety-

5 Fournier, A. Paralyse generale et syphilis, Paris, Masson et Cie, 1905.  
6 Moore, J. E. Studies in Asymptomatic Neurosyphilis. III. The Apparent Influence of Pregnancy on the Incidence of Neurosyphilis in Women, Arch Int Med 30:548 (Nov.) 1922. Also Footnote 3.

is not limited to the first two or three years of the disease, when obvious external lesions are not infrequent, but may extend over a long period of years. In Family 38 (first paper), the wife was infected by her husband, who had acquired syphilis thirteen years prior to marriage, in Family 80, infection in the husband antedated marriage by ten and one-half years. In these instances and in others which have come to our attention, the absence of demonstrable infectious lesions or a history of them in the one introducing syphilis leads to the presumption of the probability of seminal infection, although the lack of adequate experimental demonstration of the infectiousness of seminal fluid in late syphilis is recognized as a drawback to this hypothesis.

As for the course of syphilis in the partners of persons with cerebrospinal syphilis, the case is not so clear. The incidence of neurosyphilis is here only slightly higher than in an unselected group of syphilitic patients, the difference in percentages being within the limits of probable error. It is possible that diffuse cerebrospinal syphilis is caused by a second neurotropic strain of organism capable of invading the nervous system, but also prone to involve other organs, particularly at the beginning of the disease. On the other hand, it is more probable that this type of neurosyphilis may be caused by an undifferentiated strain of spirochete capable of producing lesions anywhere in the body.

Although the data submitted in this paper offer some evidence of the possible neurotropism of a strain of *Spinochaeta pallida*, it must not be forgotten that other factors in a given person or family may strongly influence the probability of parenchymatous neurosyphilis. We have offered evidence to show that familial predisposition certainly plays some rôle.<sup>11</sup> The three families reported in our second paper included eight members, all of whom acquired syphilis at different times and from different sources, yet all developed neurosyphilis. Since the publication of this paper, two additional families have come to light among our material. In the first, two brothers, acquiring syphilis from different women, at widely separated dates, have general paresis. In the second family, the father acquired syphilis in 1900 and died in 1918 of paresis, his son contracted the disease in 1919, and in 1923 has typical taboparesis. The fact that in five families such an occurrence has been observed is too striking for mere coincidence. In certain families the nervous system must be considered as a locus minoris resistentiae. This point, frequently mentioned by older syphilologists, has apparently been lost sight of in recent years.

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11 Moore, J. E., and Keidel, A. Studies in Familial Neurosyphilis. II. Familial Neurosyphilis from Various Extrafamilial Sources, J. A. M. A. 80: 818 (March 24) 1923.



Seelert<sup>10</sup> It was pointed out in our first paper that the communications from these investigators were the most satisfactory in the literature and that they differed from our own work only in their failure to employ spinal puncture as a routine method of study This omission certainly results in failure to detect an occasional case of asymptomatic neurosyphilis, so that our own percentages of conjugal neurosyphilis are throughout somewhat higher than those of any of these authors Unfortunately, no more recent studies from other clinics are available for comparison In Table 12, however, is shown a comparison of our material with the combined figures of these four writers The same discrepancies in the two group types of neurosyphilis are evident in

TABLE 12—Comparison of Author's Material with That of Four Other Authors

Type of Neurosyphilis in Person Introducing Syphilis	Reporter	Total Number of Families Examined	Number of Marital Partners Examined	Marital Partner Found to be			Percentage of Syphilitic Partners Who Were Neurosyphilitic
				Normal	Total Number Syphilitic	Certainly or Probably Neurosyphilitic	
Parenchymatous general paresis or tabes dorsalis	Combined figures of Plaut and Goring, Schachlerl, Raven, and Seelert	203	199	72	127	53	63.8
	Combined figures of Moore and Keidel and the present study	65	66	24	42	26	63.8
	Total	268	265	96	169	79	63.7
Nonparenchymatous Early or late meningovascular neurosyphilis "Cerebrospinal syphilis"	Combined figures of Schachlerl and Raven	27	27	3	24	8	88.8
	Combined figures of Moore and Keidel, and the present study	51	52	12	40	10	76.5
	Total	78	79	15	64	18	81.0

both sets of statistics and in a combination of the two Neurosyphilis is almost twice as frequent among the partners of tabetic and parietic persons as in the spouses of those with cerebrospinal syphilis

It is at least strongly indicated by these facts that parenchymatous neurosyphilis is caused by a special strain of *Spuochaeta pallida*, which invades chiefly the nervous system but is also capable of involving such other organs of the body (skin, mucous membranes or male generative apparatus) as may provide for a mode of egress, infection of others and propagation of the strain It is suggested by a study of some of our families that the infectivity of this hypothetic strain

10 Seelert, H Untersuchungen der Familienangehörigen von Paralytikern und Tabikern auf Syphilis, Monatschr f Psychiat u Neurol, 41 329, 1917

venereal spirochetosis in rabbits. It is possible to solve this problem through experimental syphilis in rabbits, but much more prolonged and careful work than has yet been done is necessary.

#### SUMMARY AND CONCLUSIONS

1 The complete routine physical, neurologic and serologic examination of 113 marital partners of 111 neurosyphilitic persons are reported.

2 Of the sixty spouses of parietic and tabetic persons, about two-thirds were syphilitic. Of these syphilitic spouses, 57 per cent were neurosyphilitic.

3 In eighteen families, the entrance of syphilis was of recent date, and one member had early cerebrospinal syphilis (clinical or asymptomatic). Fifteen of the eighteen partners had also recently acquired the infection, but, although presumably infected by the same strain causing neurosyphilis in the original member, only three of these were neurosyphilitic.

4 Among the marital partners of patients with late cerebrospinal syphilis, the incidence of syphilis was high, but that of neurosyphilis in the syphilitic partners was low (28 per cent).

5 Conjugal neurosyphilis was observed in thirty-two instances, in nine of these being detected only because of the routine use of cerebrospinal fluid examination. Conjugal neurosyphilis of the same general clinical type was comparatively frequent.

6 Although the danger of infection for the spouse increases as the date of infection in the one acquiring syphilis approaches the year of marriage, it is shown that neurosyphilitic patients may be infectious for many years, in spite of the absence of demonstrable open lesions.

7 In two thirds of the syphilitic partners of persons with parenchymatous neurosyphilis, the course of syphilitic infection had been completely latent, while among the partners of cerebrospinal neurosyphilitic persons, more than two thirds had had outspoken early or late lesions of the disease.

8 It is shown by our own material and by the data of other investigators that the incidence of neurosyphilis among the partners of persons with parenchymatous neurosyphilis is more than twice as great as in a large unselected group of women, although in the partners of persons with cerebrospinal syphilis, neurosyphilis is no more frequent than in the unselected group.

9 These data offer suggestive evidence of the existence of a neurotropic strain of *Spirochaeta pallida* as an etiologic factor in neurosyphilis of the parenchymatous type. This hypothesis does not apply to diffuse cerebrospinal syphilis, in which case evidence supporting the theory of special strain is lacking.

The influence of the kind and amount of previous treatment on the incidence of parenchymatous neurosyphilis, so well illustrated by the classical figures of Mattauschek and Pilcz,<sup>12</sup> cannot as yet be evaluated for the arsphenamin era. An interval of many years must elapse before material sufficiently large to be of value can accumulate. With regard to the data of this paper, however, it may be stated that of the syphilitic partners of neurosyphilitic patients, practically none had received any previous treatment, indeed, our examination was usually the first indication that the person had syphilis.

Such other possible etiologic factors as the influence of pregnancy,<sup>13</sup> alcoholism, stress of life and social level are, we think, fairly well controlled in our material. Even if these factors were more largely operative in our series of spouses of neurosyphilitic persons than in our unselected group of women, the differences in the incidence of neurosyphilis in the two groups could not be eliminated.

It seems to us that from the clinical standpoint, at least, the question of neurotropism cannot be solved. The statistics presented in this paper are more complete and more convincing than any heretofore published, and although we feel that further study along these same lines is of great practical value and will probably corroborate our own findings, multiplication of statistics will add little to the solution of the problem. Clinical evidence such as we present can only suggest the existence of a neurotropic strain of spirochete, absolute proof rests on experiment.

Some animal experimentation has been carried out, notably by Noguchi,<sup>14</sup> Reasoner,<sup>15</sup> Plaut and Mulzer,<sup>16</sup> and Levaditi and Marie.<sup>17</sup> The results obtained by the three first named, like our own clinical evidence, are only suggestive. The experiments carried out by Levaditi and Marie are, as we have pointed out,<sup>11</sup> together with Jahnel<sup>18</sup> and Plaut and Mulzer,<sup>16</sup> completely invalidated by the similarity of their neurotropic strain to *Spnochaeta cuniculi*, the organism of spontaneous

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12 Mattauschek and Pilcz. Zweite Mitteilung uber 4,134 katamnestisch verfolgte Falle von luetischer Infektion, Ztschr f d ges Neurol u Psychiat **15** 608, 1913.

13 Moore, J. E. Studies on the Influence of Pregnancy in Syphilis. I. The Course of Syphilitic Infection in Pregnant Women, Bull, Johns Hopkins Hosp **34** 89, 1923. Also Footnote 6.

14 Noguchi, H. Morphological and Pathogenic Variations in *Treponema pallidum*, J Exper Med **15** 201, 1912.

15 Reasoner, M. A. Some Phases of Experimental Syphilis with Special Reference to the Question of Strains, J A M A **67** 1799 (Dec 16) 1916.

16 Plaut, F., and Mulzer, P. Die Liquordiagnostik in Dienste der Experimentellen Kaninchensyphilis, Munchen med Wchnschr **69** 496, 1922.

17 Levaditi, C., and Marie, A. Etudes sur le treponeme de la paralysie generale, Ann de l'Inst Pasteur **33** 741, 1919.

18 Jahnel, F. Das Problem der progressiven Paralyse, Ztschr f d ges-Neurol u Psychiat **76** 166, 1922.

## BACTERIOLOGIC OBSERVATIONS ON ACUTE TONSILLITIS WITH REFERENCE TO EPIDEMIOLOGY AND SUSCEPTIBILITY \*

ARTHUR L BLOOMFIELD, M D

AND

AUGUSTUS R FELTY, M D

BALTIMORE

Despite the great amount of information that has been assembled on the nature of infectious disease, many fundamental problems remain unsolved. Among others, the question of just how existing balances between micro-organism and host are upset so as to lead to the spread of infection in epidemic form, demands explanation. It is clear, for example, that all cases of lobar pneumonia may be traced back ultimately to a previous case or to a pneumococcus carrier, but just how and why such a carrier will give rise to disease at one time and be harmless at another, is quite obscure. Similar considerations apply to other infections.

The lack of exact information on this question may be due in a measure to the mode of attack which has been employed, when clinical epidemiologic studies have been adequate, exact bacteriologic control has usually not been available, and, vice versa, exact bacteriologic studies have usually been conducted under conditions inadequate to give the desired epidemiologic facts. It has become apparent to students of infectious disease that the mere accumulation of masses of statistics by health boards and insurance companies, while of inestimable value, fails to explain the intimate and essential details of the spread of bacterial infection. Attempts have been made recently by several men to attack the problem by means of experimental epidemics in animals<sup>1</sup> which can be controlled both from the bacteriologic and biometric standpoint, and facts of great importance and interest have been brought out,

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\* From the Biological Division of the Medical Clinic, Johns Hopkins University and Hospital.

\* This is the second of a series of papers on streptococcus infection with special reference to acute tonsillitis.

<sup>1</sup> Amoss, H. L. J. Exper. Med. 26:25 (July) 1922. Topley, W. W. C. J. Hygiene 19:350, 1920-1921.

10 It is pointed out that other factors than strain, such as familial predisposition, treatment, pregnancy and other conditions may be operative in the etiology of neurosyphilis

11 Although the clinical evidence in favor of neurotropism offered by this paper is suggestive, it must be confirmed by adequate laboratory investigations, which are not yet available

12 The practical value of this work is self-evident. Every marital partner of a neurosyphilitic patient is himself potentially neurosyphilitic. Routine examination of the spouse by all available means, including especially study of the cerebrospinal fluid, is essential

5 General epidemiologic observations with a view to defining epidemic and sporadic disease

The present report deals with the bacteriology, and epidemiologic definition of acute tonsillitis

#### BACTERIOLOGIC OBSERVATIONS ON ACUTE TONSILLITIS

In a previous paper,<sup>2</sup> we presented the results of a survey of this experimental group of people for the presence of beta hemolytic streptococcus at a time when streptococcus disease was not prevalent. These observations, made in September and October, 1922, served as a base line with which to compare the findings in disease presented below. In brief, there were 175 controls. Of sixty-seven whose tonsils had been removed, 9 per cent showed a few scattered colonies of beta hemolytic streptococcus in the throat, whereas of 108 whose tonsils had not been removed, 37 per cent yielded the organisms, usually in large numbers, from the tonsil crypts.

In the early part of October, tonsillitis began to occur in the group, and from that time until April 1, 1923, when the experiment was concluded, there were in all thirty-nine cases.<sup>2</sup> Their distribution in relation to epidemiologic considerations will be discussed later, but it may be said now that no significant contact could be demonstrated between successive cases. All of the patients were under close observation during the attack, for the most part in the wards, and they were followed throughout the remainder of the season.

The method of study was essentially similar to that previously described in connection with the control observations<sup>3</sup> except that it did not seem advisable to probe the tonsil crypts during the acute stage of the tonsillitis. Three cultures were taken from each patient by rubbing cotton swabs over (1) the posterior pharyngeal wall, (2) the right tonsil, and (3) the left tonsil. These swabs were diluted in broth from which blood-agar plates were poured. In studying the cultures, notes were made of the predominating type of bacteria, with especial reference to beta hemolytic streptococcus, the relative and absolute numbers obtained in each culture, and the apparent identity of the various colonies of streptococci on the same plate. Several colonies were fished from each plate and preserved for study. The results of the cultures are summarized in Table 1, the first item in each case representing the culture made during the acute stage of the disease.

It was found, in the first place, that hemolytic streptococci are invariably predominant in the cultures made during the active stage of the disease. Furthermore, if cultures from the pharynx and from the

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2 The clinical features of these cases are discussed in another paper.

3 Bloomfield, A. L., and Felty, A. R. Arch. Int. Med.

however, the conditions of these experiments are so highly specialized that a certain amount of reservation must be exercised in transferring the conclusions to human infection

It seemed that if an outbreak of disease among people could be studied with an accuracy and rigidity of control approximating that attainable in an experimental epidemic, valuable information might be obtained. Such an opportunity was available in the case of a limited group of people among whom there is each winter a high incidence of acute streptococcic tonsillitis. This article concerns itself with a study of this group with the purpose, not only of obtaining exact information about the cause and epidemiology of tonsillitis, but also of deducing if possible general conclusions about the mode of spread of bacterial infection.

The group which was studied comprised approximately 200 young women—members of the training school for nurses of the Johns Hopkins Hospital. Although segregated and readily available for controlled study, conditions as regards crowding and general environment were in no way different from those which obtain in the city at large. These students are housed in several commodious buildings, not more than two live in one room, and there is free communication between the whole group and the outside world. The only occasions when more or less general contact may exist are in the dining room, in class and at the daily assembly. The general hygienic conditions are excellent.

Through the cooperation of the supervisors of nurses, it was possible to obtain cultures at any time from the members of the group, to keep accurate records of the occurrence of tonsillitis and other infections and to follow contacts.

It was assumed from our own experience as well as from observations in the literature that acute tonsillitis is usually an infection caused by hemolytic streptococci of the beta type. This supposition was confirmed by the later work, as will be pointed out. The plan of study was briefly as follows:

- 1 A detailed survey of the experimental group for hemolytic streptococci at a time when no acute streptococci disease was present.

- 2 A bacteriologic study of such cases of tonsillitis as might later occur in the group in order to determine whether (*a*) tonsillitis is an autogenous infection by a strain of streptococcus previously carried by the person, and if so, the factors which lead to a seasonal outbreak, or whether (*b*) tonsillitis is an exogenous infection due to some outside strain or strains.

- 3 The relation of carriers and of contacts to the spread of tonsillitis in the group.

- 4 The relation of season, weather, other infections, etc., to the outbreak of tonsillitis.

tonsils are compared, it is seen that the latter in practically every case yielded the bacteria in pure or almost pure culture and in tremendous numbers, whereas the pharyngeal cultures were less regular and as a rule showed many less hemolytic streptococci. This seems to indicate that the infection is primarily tonsillar, with an overflow of bacteria to the surrounding mucous membranes. Apart from the tonsil, the degree of infection seems to depend on the extent of development of lymphadenoid tissue in the throat. This is brought out by a group of six cases (Nos 23, 25, 30, 35, 36 and 38) occurring in people whose tonsils had been removed. Under these conditions the disease affected bits of lymphoid tissue which remained in the tonsillar fossae and the small nodules present behind the posterior pillars and sometimes on the posterior pharyngeal wall.

The hemolytic streptococci obtained were in every case typical of the beta group, as defined by Smith and Brown<sup>4</sup>. There was a wide (1 to 2 mm) and total zone of hemolysis about the colony without any greenish or yellowish discoloration. Furthermore, all the colonies in any one case appeared identical and whenever several were tested they gave identical reactions, although they varied somewhat in appearance in different cases. The biologic classification of the strains will be taken up in detail in another paper.

Two further points should be stressed. First, the number of hemolytic streptococci recovered bore no relationship to the severity of the clinical infection. In several cases which were mild, and which showed only slight redness and enlargement of the tonsils with swelling of the follicles and a transient rise in temperature of one or two degrees, the cultures yielded hemolytic streptococci almost pure, just as in the severe cases. In the second place, in no culture from a condition which could not be diagnosed clinically as a definite tonsillitis were real beta hemolytic streptococci recovered. It appears, therefore, that upper respiratory tract infections, especially certain types of pharyngitis, which are sometimes loosely spoken of as streptococcus throats, are not caused by real beta hemolytic streptococci, but that organism confines its activity to clinically recognizable infections of the lymphadenoid tissue, especially in the vicinity of the tonsils. Furthermore, a culture showing no beta hemolytic streptococci, if properly made, would be strong evidence against acute follicular tonsillitis and in favor of some other infection such as diphtheria or Vincent's Angina.

In a previous paper,<sup>3</sup> it was suggested that focal carriage of beta hemolytic streptococcus in the tonsil might date from a previous acute tonsillitis. This opinion was based on cultural studies of healthy controls together with their histories. It seemed of interest to check this

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4 Brown, J. H. Monograph No. 9, Rockefeller Institute, 1919



TABLE 1—Occurrence of Beta Hemolytic Streptococci in Cases of Tonsillitis During the Disease and Later

Case	Date	Days After Onset of Disease	No of Beta Hemolytic Streptococci Recovered from			Remarks
			Pharynx	Right Tonsil	Left Tonsil	
1	9/ 3/22	4	∞	∞	∞	Patient ambulatory
	9/ 8/22	9	1% of plate	Many	∞	
	1/30/23	154	2 colonies	∞*	∞*	
3	10/ 6/22	2	1 colony	∞	∞	Patient ambulatory
4	10/ 6/22	2	∞	∞	∞	
5	10/ 6/22	2	20 colonies	∞	∞	
6	1/26/23	112	10% of plate	5% of plate	5% of plate	Patient ambulatory
	10/ 7/22	2	50% of plate	∞	∞	
	10/ 9/22	2	Many	∞	∞	
7	10/18/22	11	30% of plate	∞	∞	Patient ambulatory
	1/23/22	109	None	20 colonies*	None*	
	10/ 9/22	2	Many	∞	∞	
8	10/16/22	9	Many	∞	∞	Patient ambulatory
	1/24/23	110	None	None*	1 colony*	
	1/26/23	112	None	None*	None*	
9	10/18/22	2	10% of plate	∞	∞	Patient ambulatory
	1/23/23	97	None	Many	None	
	10/17/22	2	None	∞	∞	
10	1/24/23	99	None	∞*	2 colonies*	Patient ambulatory
	10/30/22	4	Many	∞	∞	
	11/13/22	3	∞	∞	∞	
11	1/24/23	78	None	Many*	Few*	Patient ambulatory
	10/19/22	2	Many	Many	Many	
	1/23/23	64	None	2 colonies*	None*	
14	11/23/22	2	None	∞	∞	Patient ambulatory
	1/23/23	61	None	None*	None*	
	11/23/22	2	∞	∞	∞	
15	1/23/23	61	1 colony	∞*	½ of plate	Patient ambulatory
	11/25/22	2	∞	∞	∞	
	12/ 2/22	2	25% of plate	∞	∞	
16	1/30/23	61	None	6 colonies*	None*	Patient ambulatory
	12/ 6/22	2	∞	∞	∞	
	12/ 9/22	2	Many	∞	∞	
19	1/23/23	55	1 colony	50% of plate*	∞*	Patient ambulatory
	1/ 4/23	3	∞	∞	∞	
	1/ 5/23	2	—	∞	∞	
22	1/ 6/23	2	∞	∞	∞	Tonsillectomy 11/21
	1/ 6/23	2	∞	∞†	∞†	
	3/20/23	73	None	None†	None†	
24	1/ 6/23	2	∞	∞	∞	Patient ambulatory
	1/12/23	2	∞	50% of plate†	—	
	1/23/23	13	Few	50% of plate†	30% of plate†	
26	3/20/23	67	None	2 colonies†	None†	Patient ambulatory
	1/19/23	2	∞	∞	∞	
	1/22/23	3	∞	∞	∞	
27	1/23/23	4	∞	∞	∞	Patient ambulatory
	1/24/23	5	∞	∞	∞	
	1/24/23	3	Many	∞	∞	
29	1/25/23	2	—	∞	∞	Tonsillectomy 8 yrs ago
	1/21/23	1	∞	∞†	∞†	
	1/29/23	2	∞	∞	∞	
32	2/19/23	2	∞	∞	∞	Picture not as out spoken as usual
	2/19/23	2	50% of plate	50% of plate	50% of plate	
	2/26/23	4	None	Many	Many	
35	2/26/23	2	∞	∞†	∞†	Tonsillectomy 6 yrs ago
	3/20/23	24	None	None†	None†	
	2/26/23	2	∞	∞†	∞†	
36	3/20/23	24	None	5% of plate†	5% of plate†	Patient ambulatory
	2/27/23	2	∞	∞	∞	
	3/ 2/23	2	∞	∞†	∞†	
37	3/ 4/23	2	∞	∞	∞	Tonsillectomy 1 year ago
	3/ 9/23	2	∞	∞	∞	
			∞	∞	∞	

∞ indicates innumerable and almost pure culture, \*, crypt culture, †, culture from tonsil fossa

TABLE 2—Duration of Persistence of Beta Hemolytic Streptococcus in Tonsil Crypts Following Acute Tonsillitis

Days After Onset of Acute Infection That Culture Was Made	No. of Cases	Beta Hemolytic Streptococcus		Remarks	
		Present	Absent		
Nontonsillectomized Cases					
125-154	1	1	0	Only 2 colonies recovered	
100-125	4	3	1		
75-100	3	3	0		
50- 75	5	5	0		
0- 50	40	40	0		
Tonsillectomized Cases					
73	1	0	1		
67	1	1	0		
24	2	1	1		
13	1	1	0		
0-5	6	6	0		

TABLE 3—Relation of Occurrence of Acute Streptococcal Tonsillitis to Previous Streptococcus Carrier State

Case	Control Culture for Hemolytic Streptococcus		Culture During Acute Tonsillitis		Days Between Control Culture and Onset of Tonsillitis
	Date	Result	Date	Result	
1	Not made		8/30/22	Positive	
3	Not made		10/ 6/22	Positive	
4	9/23/22	Negative	10/ 6/22	Positive	11
5	9/30/22	Negative	10/ 6/22	Positive	6
6	Not made		10/ 7/22	Positive	
7	Not made		10/ 9/22	Positive	
8	Not made		10/ 9/22	Positive	
9	9/12/22	Negative	9/18/22	Positive	36
10	9/ 7/22	Negative	10/17/22	Positive	40
11	9/23/22	Negative	10/29/22	Positive	36
12	10/20/22	Negative	11/11/22	Positive	22
13	9/ 1/22	Positive	11/14/22	Positive	74
14	10/16/22	Negative	11/23/22	Positive	38
15	10/18/22	Negative	11/23/22	Positive	36
16	10/10/22	Negative	11/25/22	Positive	46
17	9/17/22	Negative	12/ 2/22	Positive	76
18	10/20/22	Negative	12/ 6/22	Positive	47
19	10/16/22	Negative	12/ 9/22	Positive	54
20	10/12/22	Negative	1/ 4/23	Positive	84
21	9/29/22	Negative	1/ 5/22	Positive	98
22	9/ 7/22	Negative	1/ 5/23	Positive	110
23	10/10/22	Negative	1/ 6/23	Positive	88
24	9/30/22	Negative	1/ 6/23	Positive	98
25	10/18/22	Negative	1/12/23	Positive	86
26	9/21/22	Negative	1/19/23	Positive	120
27	9/ 7/22	Negative	1/12/23	Positive	127
28	10/26/22	Negative	1/22/23	Positive	98
29	9/12/22	Negative	1/25/23	Positive	145
30	10/10/22	Negative	1/29/23	Positive	111
31	10/20/22	Negative	1/29/23	Positive	101
32	9/25/22	Negative	2/19/23	Positive	147
33	10/16/22	Negative	2/21/23	Positive	128
34	10/ 9/22	Negative	2/23/23	Positive	137
35	10/ 5/22	Negative	2/24/23	Positive	142
36	9/15/22	Negative	2/26/23	Positive	164
37	10/ 9/22	Negative	2/27/23	Positive	141
38	10/ 5/22	Negative	3/ 2/23	Positive	148
39	9/15/22	Negative	3/ 4/23	Positive	170
40	10/20/22	Negative	3/ 9/23	Positive	170

point further by studying convalescents for the persistence of beta hemolytic streptococcus Brown,<sup>4</sup> working with surface throat cultures, found that early in convalescence from acute tonsillitis the real beta hemolytic types of streptococcus began to disappear and were replaced by alpha prime, alpha and green producing types A truer idea of persistence can, however, be obtained by cultures of aspirated crypt material Such a method applied in the present series showed that real beta hemolytic streptococcus persisted in the tonsils for long periods of time, although the pharynx cultures yielded only a few or none of the organisms A transition took place from conditions found in the acute infection to a focal tonsillar carriage On the other hand, in the six cases of acute streptococcus lymphadenoid infection in subjects whose tonsils had been removed, the organisms diminished and disappeared with relative rapidity The exact biologic relationship of streptococci recovered after various intervals from convalescents to the disease strain will be discussed in detail later, but it may be said now that a strain recovered as late as 154 days was identical with the original culture made during the acute attack

The details of the recultures are given in Table 1 and are summarized in Table 2 Of fifty-three cultures in nontonsillectomized cases made up to the one hundred and fifty-fourth day, only one was negative (on the one hundred and twelfth day), whereas of eleven cultures made in tonsillectomized cases up to the seventy-third day, two had become negative (seventy-third day, twenty-fourth day), and one showed only two colonies (sixty-seventh day) It appears, then, that real beta hemolytic streptococci may persist in the tonsil for an indefinite length of time after acute tonsillitis, but dies out rapidly on the free mucous membranes of the throat

#### RELATION OF OCCURRENCE OF TONSILLITIS TO PREVIOUS CARRIER STATES

One of the main objects of the present study was to determine whether acute tonsillitis is usually an autogenous infection from a strain already carried in the tonsils or whether it represents invasion by a fresh outside strain Control cultures had been made in the experimental group When cases of tonsillitis later began to appear it soon was obvious that the infection occurred in those who previously had not been carriers of beta hemolytic streptococcus, whereas the carriers with one exception failed to develop acute tonsillitis These facts are summarized in Table 3 It appears that of thirty-four people who developed tonsillitis, only one was previously a carrier of the beta hemolytic streptococcus The interval between negative control culture and onset

4 No special clinical or bacteriologic association could be demonstrated between successive cases of tonsillitis in the present group

It remains, then, to attempt to place the present outbreak in a proper epidemiologic setting. Among the 175 members of the group there occurred, during six months, thirty-nine cases of tonsillitis—a rate of 22 per cent. A similar incidence of typhoid fever, scarlet fever or many other acute infectious diseases would stimulate more serious consideration than a mild disease such as tonsillitis, but the problem remains of no less interest from a purely epidemiologic standpoint. In brief, the point which it seemed desirable to settle was whether the present outbreak represented a true epidemic or merely a large group of sporadic cases.

If one considers the feature of extensive outbreaks of acute infectious disease which may be regarded as truly epidemic, two points are outstanding. First, there is invariably evidence of direct spread from person to person, second, if the exciting cause is a readily demonstrable

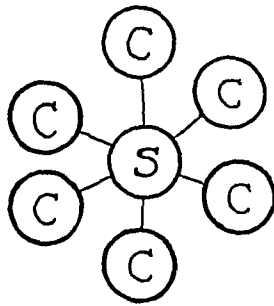


Fig 2—Mass infection

or some alteration in the type of parasitism of the organism in the community as a whole can be determined. In a fulminating epidemic of meningitis, for example, there is clinical evidence of contact between patients and also a great increase in the general meningococcus carrier rate even among healthy noncontacts. The epidemic, in short, is associated with a fundamental upset in the "normal" type of parasitism of the causal organism. A similar state of affairs has been found in highly epidemic streptococcus infection in the military camps, in diphtheria and other infections.

In contrast to the foregoing, a widespread outbreak from a common source which is not an epidemic is shown in Figure 2.

The condition represented in Figure 2 might be illustrated by a water-borne outbreak of typhoid fever.

In sporadic disease, on the other hand, in its purest form conditions are quite different from those obtaining in a true epidemic. There is no spread from case to case, but each instance of the disease arises from a distinct source, such as a chronic carrier. Furthermore, there is no

of disease varied from five to 170 days. The briefer intervals are of interest in so far as they may indicate that the streptococcus is not carried for any length of time before disease occurs.

In summary, then, in the present series tonsillitis was distinctly not an autogenous infection but resulted from invasion by an outside strain. The strains concerned were not identical but, as will be shown later, fell into several groups.

It would be of great interest to determine the time of acquisition of the beta hemolytic streptococcus in relation to the onset of acute tonsillitis in a number of cases, but this could only be done by making frequent cultures in a susceptible group. By chance a single observation was made which may be mentioned. In Case 31 a control culture was made on Oct 18, 1922, which yielded no beta hemolytic streptococci. On Jan 31, 1923, this patient entered the ward with a typical attack of influenza. A throat culture now showed a few scattered colonies of

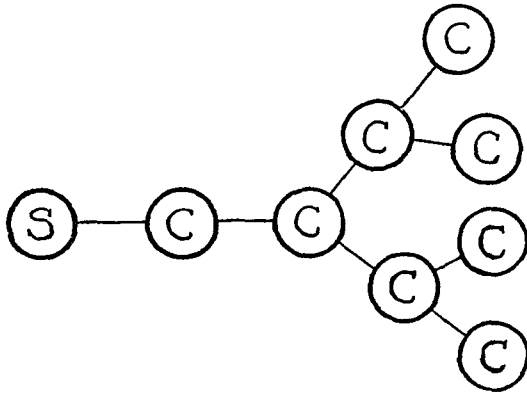


Fig 1—The essential features of an epidemic. In this and in the following illustrations, S represents source and C case or carrier.

the beta hemolytic streptococcus. There were no symptoms or evidence of tonsillitis. On the following day, she developed a mild but definite acute follicular tonsillitis. Culture now showed innumerable beta hemolytic streptococci in practically pure culture from both pharynx and tonsils. In this case at least, the advent of the organism preceded the onset of the disease.

#### EPIDEMIOLOGIC DATA

In the preceding sections, certain facts have been presented which may be briefly summarized.

- 1 Acute tonsillitis in the present group of cases was invariably an infection with beta hemolytic streptococci.
- 2 The disease affected almost uniformly a group of people who were not previously carriers of this organism.
- 3 Carriers, although equally exposed, did not develop acute tonsillitis, except in one case.

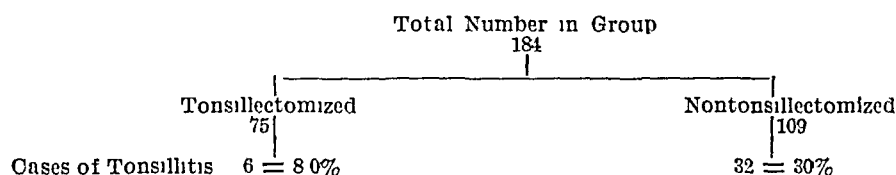
Figure 3 One might picture, on the one hand, a variety of possible sources of infection (carriers) in close contact with a group of susceptible people on the other. The exact nature of susceptibility cannot be defined completely as yet, but in the present instance it has been possible to determine at least three factors, which will be discussed in the following section

#### FACTORS CONCERNED IN RESISTANCE TO ACUTE TONSILLITIS

An attempt was made to analyze further the factors which seemed to promote infection on the one hand or to decrease susceptibility on the other

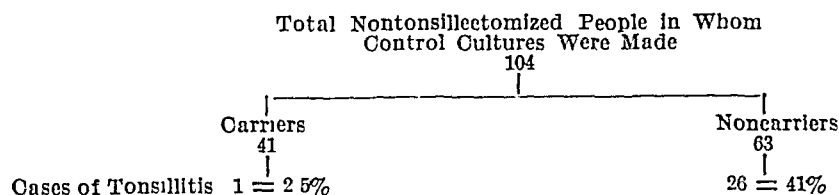
1 Relation of tonsillectomy to occurrence of acute streptococcic lymphadenoid infection of the throat. It soon became apparent that the incidence of infection was lower in those members of the group whose tonsils had been removed. Of the 184 subjects, 109 possessed their tonsils, whereas in seventy-five cases, they had been removed. Among the former there were thirty-two instances of tonsillitis, an incidence of 30 per cent, among the latter, there were six cases, an incidence of 8 per cent.

The occurrence of "tonsillitis" in tonsillectomized and nontonsillectomized members of the group is represented below



It appears, then, that tonsillectomy definitely renders a person less susceptible to acute streptococcic infection of the lymphadenoid tissue of the throat, and the explanation seems obviously an anatomic one.

2 The relation of the streptococcus carrier state to susceptibility to tonsillitis. As pointed out above, it was striking that those persons who already were tonsil carriers of the human type beta hemolytic streptococcus failed to develop tonsillitis during the course of the present experiment except in one instance. The incidence of tonsillitis in carriers and noncarriers is presented graphically in the diagram.



It appeared, therefore, that streptococcus carriage furnished a sound index of the likelihood of a person developing tonsillitis. The question remained open, however, whether the presence of the streptococcus in

evidence of any alteration in the general state of parasitism of the exciting organism in the community at large. Special susceptibility of the person is important rather than (possible) increased virulence of the bacteria. Figure 3 illustrates pure sporadic disease.

Obviously there are transition stages between pure sporadic and true epidemic disease in which a variety of sources may give rise to small groups of cases, no individual unit acquiring great potential.

In the present outbreak of tonsillitis these possibilities deserved consideration.

1 A true epidemic with spread from case to case. This possibility was ruled out by (a) absence of demonstrable clinical contact between successive or coincident cases, and (b) by the variety of strains of streptococcus concerned.

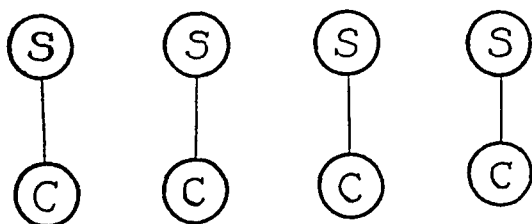


Fig 3—Pure sporadic disease

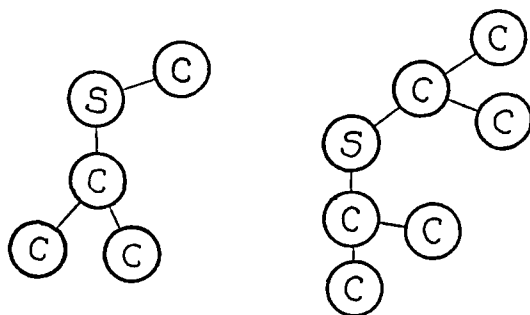


Fig 4—Transition stages between pure sporadic and true epidemic disease

2 A common infection from a single source such as a carrier. This possibility was ruled out by the multiplicity of strains.

3 Infection of successive persons from a series of distinct sources, such as a group of carriers. This was undoubtedly the case in the present outbreak, as is shown by the following facts:

1 The known presence in the group of a large number of potential sources of infection in the form of chronic streptococcus carriers.

2 The absence of evidence of contact between cases.

3 The fact that a variety of strains (at least four) were concerned with the production of the disease.

4 The absence of any alteration in the general type of streptococcus parasitism in the group as a whole when streptococcus disease became prevalent as has been pointed out in a previous paper.<sup>1</sup>

In brief, then, despite the large number of cases, the outbreak consisted of multiple instances of sporadic infection, as illustrated in

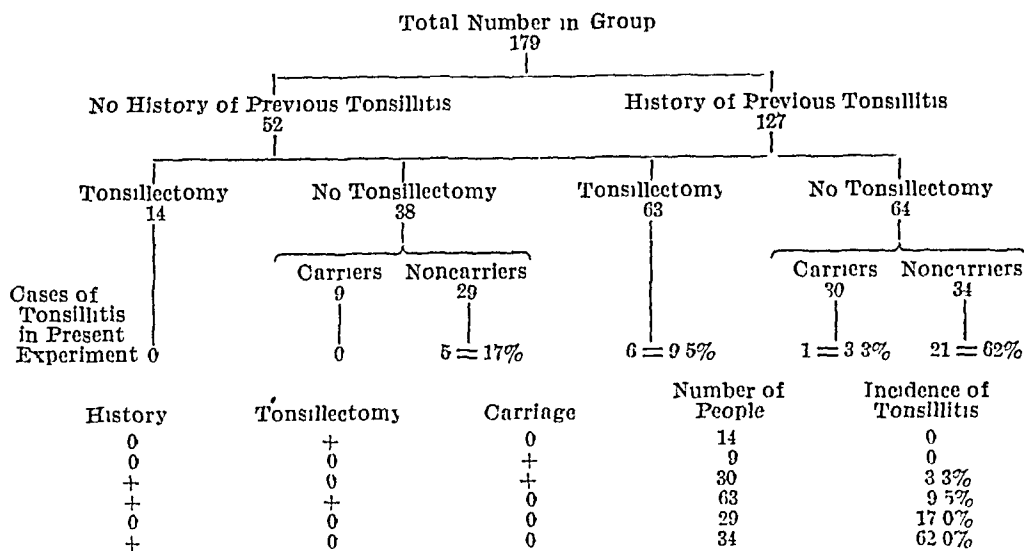
expressed by saying that if a person reaches the age of 20 years (approximately) without having had tonsillitis, the chances of acquiring the infection later are relatively slight

The entire question of susceptibility, as brought out in the present study, may then be summarized as follows In a group of young adults there are a certain number who seem to be "naturally" insusceptible or relatively insusceptible to acute streptococcic infection of the lymphoid

TABLE 4—Interval Between Present and Previous Attack of Tonsillitis

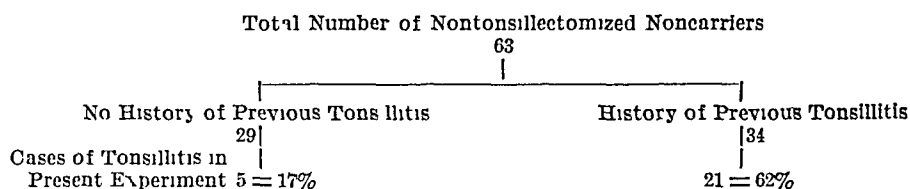
Case	Previous Attack	Present Attack	Interval
19	August, 1922	December, 1922	4 months
13	February, 1922	November, 1922	9 months
10	November, 1921	October, 1922	11 months
24	1922	1923	12 months
32	February, 1922	February, 1923	12 months
39	November, 1921	March, 1923	16 months
37	October, 1921	February, 1923	17 months
34	October, 1921	February, 1923	17 months
22	March, 1921	January, 1923	22 months
31	February, 1921	February, 1923	2 years
14	1920	1922	2 years
15	1920	1922	2 years
28	1919	1923	4 years
1	1917	1922	5 years
27	1913	1923	10 years
29	1913	1923	10 years
11	1908	1922	14 years
26	Childhood	1922	15 plus years
16	"Years ago"	1922	? years
4	"None recently"	1922	? years

tissue in the throat Such insusceptibility is enhanced by tonsillectomy, and in any case tonsillectomy confers a high degree of protection Among people not naturally insusceptible, a temporary protection is conferred by the carriage of streptococcus following an acute infection The subsidence of the carrier state in this group is, however, followed by a prompt increase in susceptibility All the factors are assembled in the following diagram





itself conferred protection, or whether the streptococcus merely indicated some other or previous reaction, such as an attack of tonsillitis, which had led to the development of a certain degree of immunity. It was decided to test the latter hypothesis on the following supposition: If the presence of streptococcus in itself was not responsible for protection, and if lack of susceptibility were due to protection conferred by passing through an attack of tonsillitis of which the streptococcus was merely an indication, then the more recent the attack of tonsillitis the greater one would expect the protection to be. The group of sixty-three nontonsillectomized noncarriers was therefore analyzed in regard to the relation of history of previous tonsillitis to occurrence or non-occurrence of tonsillitis during the course of the present experiment. The results are shown in the following diagram:



The results are the opposite of what would be expected if the previous attack of tonsillitis conferred protection apart from continued carriage of streptococcus. In other words, of those people who are not carriers at a given time, those who have never had tonsillitis and therefore have probably never been carriers are less susceptible; conversely, it must be concluded that in so far as insusceptibility runs parallel to streptococcus carriage such insusceptibility must depend directly on the presence of the streptococcus. One may think of the carried organisms as keeping up a sort of chronic vaccination, the protective effects of which wear off rapidly when the carriage ceases. This view is supported by the facts presented in Table 4, which shows the interval elapsing between the present attack and the preceding one. It is seen that in a good many cases the streptococci had disappeared and immunity had worn off within a few months to two years after the previous attack.

3 "Natural" resistance. A further examination of the diagram indicates that people with no history of tonsillitis in the past showed much less tendency to develop the disease in the present experiment than a similar group with positive past history. This would seem to mean that certain persons possess naturally a lower degree of susceptibility to this type of streptococcus infection than others. Whether this relative degree of immunity is inherent and natural, whether it is acquired in an unrecognizable way, or whether it depends on anatomic conditions, it does not seem profitable to discuss at the present time. At any rate, the fact is definite, and for clinical purposes may best be

# ELECTROCARDIOGRAPHIC CHANGES FOLLOWING OCCLUSION OF THE LEFT CORONARY ARTERY \*

FRED M SMITH, M D

CHICAGO

In 1918, an investigation<sup>1</sup> was reported in which an electrocardiographic study was made on the dog following the ligation of the coronary arteries. The changes in the T-deflection subsequent to the closure of branches of the left coronary artery were the most constant findings. Immediately following the ligation, this deflection became more prominent, and the height that it assumed apparently depended on the degree to which the circulation to the left ventricle was disturbed. After the closure of the descending or circumflex branches the amplitude of the T-wave occasionally approached and in a few instances even exceeded that of the R-deflection. The increase in the amplitude of the T-wave has repeatedly been observed in later work in which it was necessary to ligate branches of the left coronary artery.

Within twenty-four hours the T-deflection became sharply negative. The extent to which this wave became a negative phase and the duration of this state likewise seemed to depend on the size of the vessel ligated. Following the closure of either of the main branches of the left coronary artery, the T-wave usually became negative in each of the three leads and remained in this condition for three or four days. The extent of the downward deflection gradually became less, and by the sixth or eighth day had changed to a positive phase in lead I, later in lead II and finally in lead III. The order of the derivations in which the T-wave changed to an upward deflection was occasionally reversed.

The negative feature of the T-deflection was checked up in a subsequent investigation<sup>2</sup>. In those instances in which the T-wave failed to become negative following the ligation of branches of the left coronary artery there was an extensive collateral circulation which had almost eliminated the formation of an area of infarction.

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\* Read before the American Society for Clinical Investigation, Atlantic City, N J, April 30, 1923

\* From the Department of Medicine of Rush Medical College and the Presbyterian Hospital

1 Smith, Fred M. The Ligation of Coronary Arteries with Electrocardiographic Study, Arch Int Med **22** 8 (July) 1918

2 Smith, Fred M. Further Observations on the T-Wave of the Electrocardiogram of the Dog Following the Ligation of the Coronary Arteries, Arch Int Med **25** 673 (June) 1920

## SUMMARY

1 In the present series of cases acute follicular tonsillitis was uniformly due to the beta hemolytic type of streptococci

2 Following the acute disease, the organisms persist for an indefinite length of time in the tonsils

3 Evidence is presented to show that a large outbreak of tonsillitis was not a real epidemic but a group of sporadic cases

4 Tonsillectomy confers a high degree of protection against acute streptococcic infection of the lymphoid tissue of the throat

5 A certain number of persons in a group seem "naturally" insusceptible or relatively insusceptible to tonsillitis

6 Tonsillitis is not as a rule an autogenous infection but occurs in people not already carriers of hemolytic streptococci

leads Two of the patients studied by Robinson and Herimann gave electrocardiograms in which the final ventricular deflection was negative after the coronary accident In the one whom frequent curves were taken, the transition in the form of the T-wave was similar to that produced experimentally in the dog

Wearn<sup>7</sup> has recently reported a study of nineteen cases of cardiac infarction which came to necropsy In ten, electrocardiograms were taken In eight, only one record was made Wearn noted that the disturbance in the T-wave and a decrease in the amplitude of the QRS deflections were the most constant findings In all ten patients there was an alteration of the T-wave in at least one lead He particularly mentioned the frequency of the change in this deflection in leads I and II In one, the T-wave in lead II arose from the descending limb of the R-deflection as in the patient reported by Pardee This curve was taken on the first day after the onset of the cardiac accident

The amplitude of the QRS waves was diminished in the curves of five of the ten patients In some instances this feature was so marked that the deflections were almost iso-electric

#### CORONARY OCCLUSION IN MAN

This report is based on the electrocardiographic findings of eleven patients In one, the descending branch of the left coronary artery was ligated in the repair of a self-inflicted stab wound of the heart The remaining ten had the typical clinical manifestations of coronary artery occlusion In two the diagnosis was verified at necropsy Eight recovered from the attack In eight of these eleven patients, three or more electrocardiograms were taken

CASE 1—H S,<sup>8</sup> aged 44, entered the Cook County Hospital on Aug 3, 1920 Shortly after entering the hospital he attempted suicide by stabbing himself in the precordial region with a sixteen penny casing nail He was found by the intern in a state of collapse and rushed to the operating room Dr George L Davenport exposed the heart under local anesthesia and found blood spurting from a wound in the heart just to the left of the descending branch of the left coronary artery at the level of the middle third In the repair of the wound Dr Davenport found it necessary to ligate the artery The patient made an uneventful recovery On the nineteenth day following the operation the patient reported to the Presbyterian Hospital for an electrocardiogram The T-wave (Fig 1 *a*) was negative in each of the three leads The second curve (Fig 1 *b*) was taken seventeen days later The final ventricular deflection was less negative The third electrocardiogram (Fig 1 *c*), which was taken fifty-nine days after the operation, was similar to the second The fourth record was made nine months after the operation At this time the T-wave was a positive phase in the leads I and II

7 Wearn, J T Thrombosis of the Coronary Arteries with Infarction of Heart, *Am J M Sc* **165** 25, 1923

8 This patient is to be reported more in detail by Dr Davenport

The decrease in the amplitude of the QRS group that followed the ligation of the branches of the left coronary artery was only casually mentioned in the first report. The curves taken during this investigation have since been reviewed. It was noted that ten animals recovered from the ligation of the descending branch, six the circumflex branch of the left coronary artery and thirteen the combined closure of one or more branches of these two vessels. The electrocardiograms of twelve showed a diminished amplitude of the QRS group. This change in the electrocardiogram followed the closure of the circumflex in six (100 per cent), the descending branch of the left coronary in two (20 per cent) and the branches of each of these arteries in four (30 per cent).

The change in the amplitude of the initial ventricular deflections was observed as early as the second day after the operation. In some it persisted until necropsy. In others the height of the deflections gradually returned to normal after two or three weeks.

During the time of the initial investigation, a patient consulted Dr. Herrick,<sup>3</sup> in whom he made a diagnosis of coronary thrombosis which was later verified by necropsy. This patient was first seen fifteen days following the coronary accident. The electrocardiogram showed a sharp negative T-deflection in leads I and II. Ten days later the T-wave was less negative in leads I and II. In the curve taken after a period of five months the amplitude of the QRS group was very low. In the meantime, the patient had another attack of severe precordial pain which lasted for several hours. At necropsy the descending branch of the left coronary artery and one of the main descending branches of the circumflex were occluded. The thrombosis of the latter vessel was of recent origin. There was an extensive fibrosis of the endocardial and subendocardial layers which extended from the apex upward and involved the papillary muscles.

Since Dr. Herrick's report, Pardee,<sup>4</sup> Robinson and Herrmann<sup>5</sup> and Kahn<sup>6</sup> have observed changes in the T-deflection following coronary occlusion in man. The initial electrocardiogram was taken of the patient reported by Pardee about two hours after the onset of the cardiac pain. The T-wave was very prominent in leads II and III and arose from the descending limb of the R-peak. A few days later the T-deflection was a sharply negative phase in the corresponding

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3 Herrick, J. B. Thrombosis of the Coronary Arteries, *J. A. M. A.* **72** 387 (Feb. 8) 1919.

4 Pardee, H. E. B. An Electrocardiographic Sign of Coronary Artery Obstruction, *Arch. Int. Med.* **26** 224 (Aug.) 1920.

5 Robinson, G. C., and Herrmann, G. R. Paroxysmal Tachycardia of Ventricular Origin, and Its Relation to Coronary Occlusion, *Heart* **8** 59, 1921.

6 Kahn, M. H. Aneurysm of the Left Ventricle, *Am. J. M. Sc.* **163** 839, 1922.

CASE 2—M F, aged 51, entered the Presbyterian Hospital in the service of Dr Irons on Jan 25, 1923. He complained of severe precordial pain and shortness of breath. He stated that the pain first appeared while on the way to his business about 9:30 in the morning. It became so severe that he was compelled to stop in a drug store for relief. While here he collapsed and was taken to the hospital. When he reached the hospital the pain was very severe and radiated to both arms. There was in addition to the pain a sensation of great heaviness and constriction in the chest. He was compelled to sit up because of the shortness of breath. The patient was seen by Dr Irons soon after he entered the hospital, about 11:30 a. m. He was given, hypodermatically, morphin sulphate,  $\frac{1}{4}$  grain. The pain, however, continued through the afternoon and evening and morphin was repeated. Shortly following the second hypodermic administration of morphin the patient went to sleep and had a fairly good night. He, however, awakened in the morning with the same precordial distress. It gradually became less severe during the morning and had entirely disappeared by 10:30.

When the patient was first seen by Dr Irons the pulse rate was about 90 per minute, and the quality was fair. The left cardiac dulness was slightly outside the midclavicular line. The heart tones were faint. There was no definite murmur, and the rhythm was regular. The following morning the patient had a short attack of rapid but regular action of the heart. Soon after the attack the heart was examined. A definite systolic apical murmur was noted. The left cardiac dulness was well outside the midclavicular line. The other physical findings were negative.

The first electrocardiogram (Fig 2, *a*) was taken at 4:45 p. m. of the same day that the patient entered the hospital. The T-wave was slightly negative in the first lead. The following morning at 9:30 the T-deflection (Fig 2, *b*) was markedly negative in lead I and iso-electric in lead II. A curve (Fig 2, *c*) taken at 2:30 p. m. on the second day showed sharply negative T-waves in the first and second leads. There was at this time a definite decrease in the amplitude of the QRS-deflections. The following day the T-wave (Fig 2, *d*) was still negative in lead I but had changed to an iso-electric state in lead II. The amplitude of the QRS group had increased. The curves (Fig 2, *e* and *f*) taken on the two succeeding days were similar to the latter. At this time the patient had begun to feel better, and left the hospital against the advice of the physician.

CASE 3—A D L, aged 39, entered the Presbyterian Hospital on Feb 15, 1922, in the service of Dr Vernon David for hemorrhoidectomy. The following morning while in the operating room he experienced a severe pain in the sub-sternal region, associated with a feeling of heaviness. The distress gradually increased in intensity and radiated to the arms. The pulse became rapid and irregular. The pain continued until the following morning. During this time the patient had received heroin hydrochlorid,  $\frac{1}{2}$  grain, morphin sulphate,  $\frac{1}{6}$  grain, and several doses of nitroglycerin,  $\frac{1}{100}$  grain, without complete relief from the distress. He was seen at this time by Dr Dick. The left cardiac dulness was well outside the midclavicular line. A soft systolic apical murmur was heard, and there was a gallop rhythm. The cardiac rate was 130 a minute. A diagnosis of probable coronary occlusion was made. The cardiac findings remained about the same for the following ten days, except for periods of marked irregularity which were apparently due to the frequent appearance of premature contractions. During this time there was an occasional complaint of precordial distress. On March 4, the gallop rhythm had disappeared. There was still a short murmur over the apical area. The patient seemed to feel well and was permitted to sit up on a back rest. Four days later he died while asleep. At necropsy the descending branch of the left coronary artery and two of the smaller branches of the circumflex were found occluded. The pathologic findings in the layers of the myocardium were essentially the same as in the patient whose case was reported by Dr Herrick.

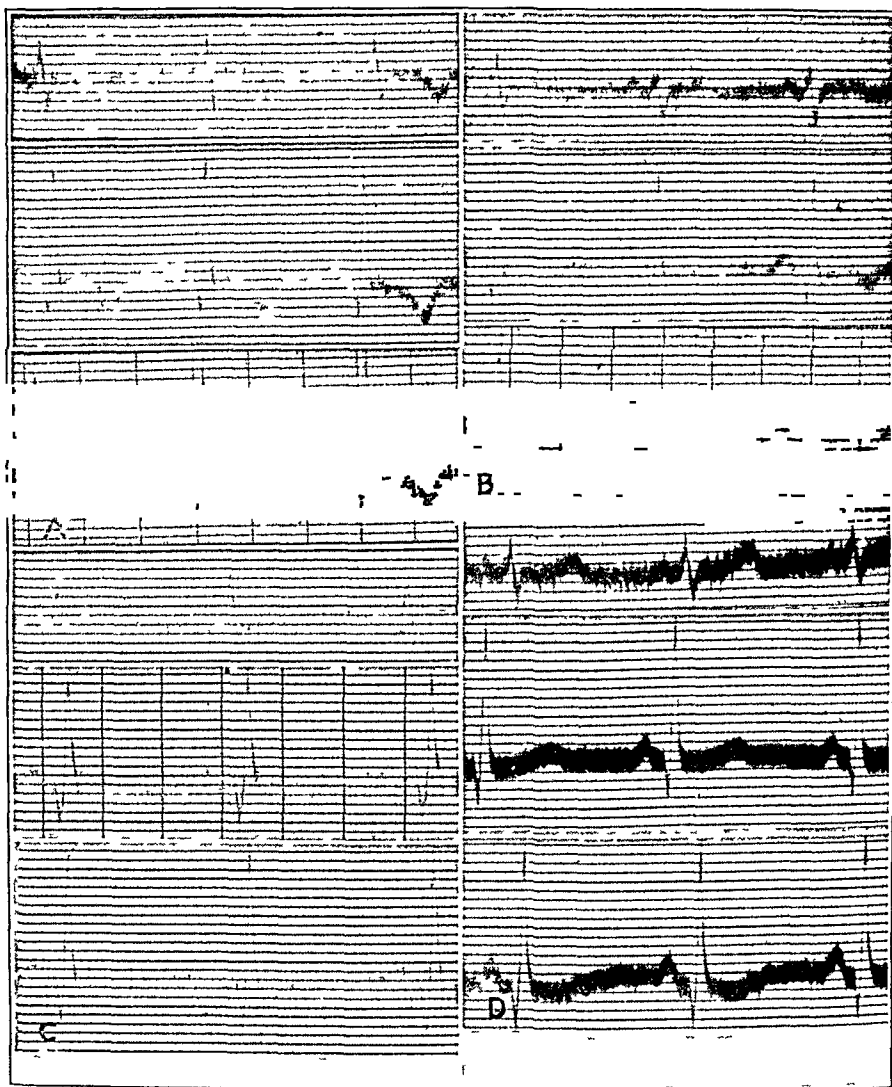


Fig 1 (Case) 1—*a*, electrocardiogram taken nineteen days after the ligation of the descending branch of the left coronary artery. The T-wave is a sharply negative deflection in the three leads, *b*, taken thirty-six days following the operation. The T-wave is less negative than in the previous curve, *c*, taken fifty-nine days after the ligation. The T-deflection is still slightly negative, *d*, curve taken eight and one-half months following the ligation. The final ventricular deflection has changed to a positive phase in leads I and II and to an iso-electric state in lead III.

The first electrocardiogram (Fig 3, *a*) was taken on the morning following the onset of the pain. He still had distress. The curve showed what is ordinarily considered a right bundle branch conduction defect. The T-wave was diaphasic in lead I and moderately prominent in leads II and III. Three days later the T-deflections (Fig 3, *b*) were iso-electric in the three leads. The T-wave in the curve taken eleven days after the second record (Fig 3, *c*) was negative in the first and second leads and the amplitude of the QRS group markedly diminished.

CASE 4—G B M., aged 42, entered the Presbyterian Hospital on Nov 8 1921, in the service of Dr Irons. A few days prior to entering the hospital the patient had had a series of attacks of severe precordial pain which radiated to the arms and neck. These attacks apparently came on without exertion or excitement. The last appeared shortly after eating lunch, and

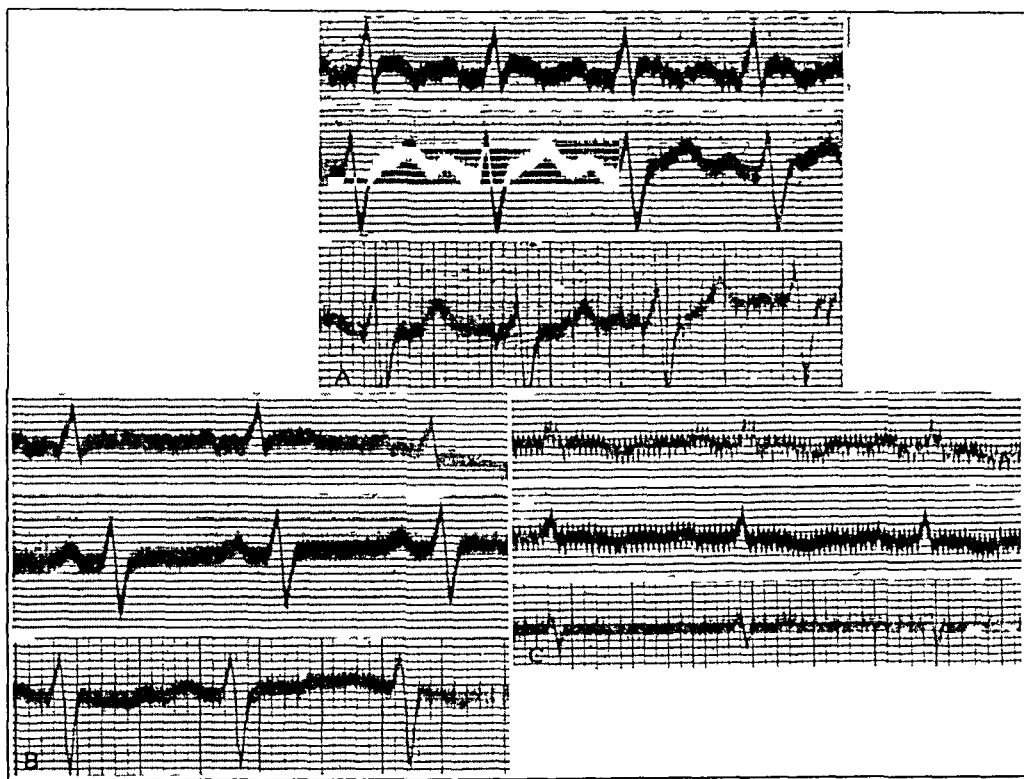


Fig 3 (Case 3)—*a*, in this patient the diagnosis of coronary thrombosis was verified by necropsy. The curve was taken twenty-four hours after onset of cardiac pain. The patient still had pain at the time the record was made. The electrocardiogram resembles that of a right bundle branch block, *b*, taken four days following the cardiac accident. The T-wave is practically iso-electric in the three leads. There has been little change in the other ventricular deflection, *c*, taken eleven days later, fifteen days after onset of pain. The amplitude of the QRS group is markedly diminished. The T-deflection is negative in leads I and II.

the patient became nauseated. In one attack, the distress lasted for about sixteen hours. Following the last attack the patient felt weak and the heart became rapid. Two days later he came to the hospital. At this time he was short of breath on the slightest exertion. The left cardiac dulness was just inside the anterior axillary line. There was a systolic apical murmur, and the rhythm was frequently interrupted by premature beats. A friction rub was noted over the lower sternum. The systolic blood pressure was 102,



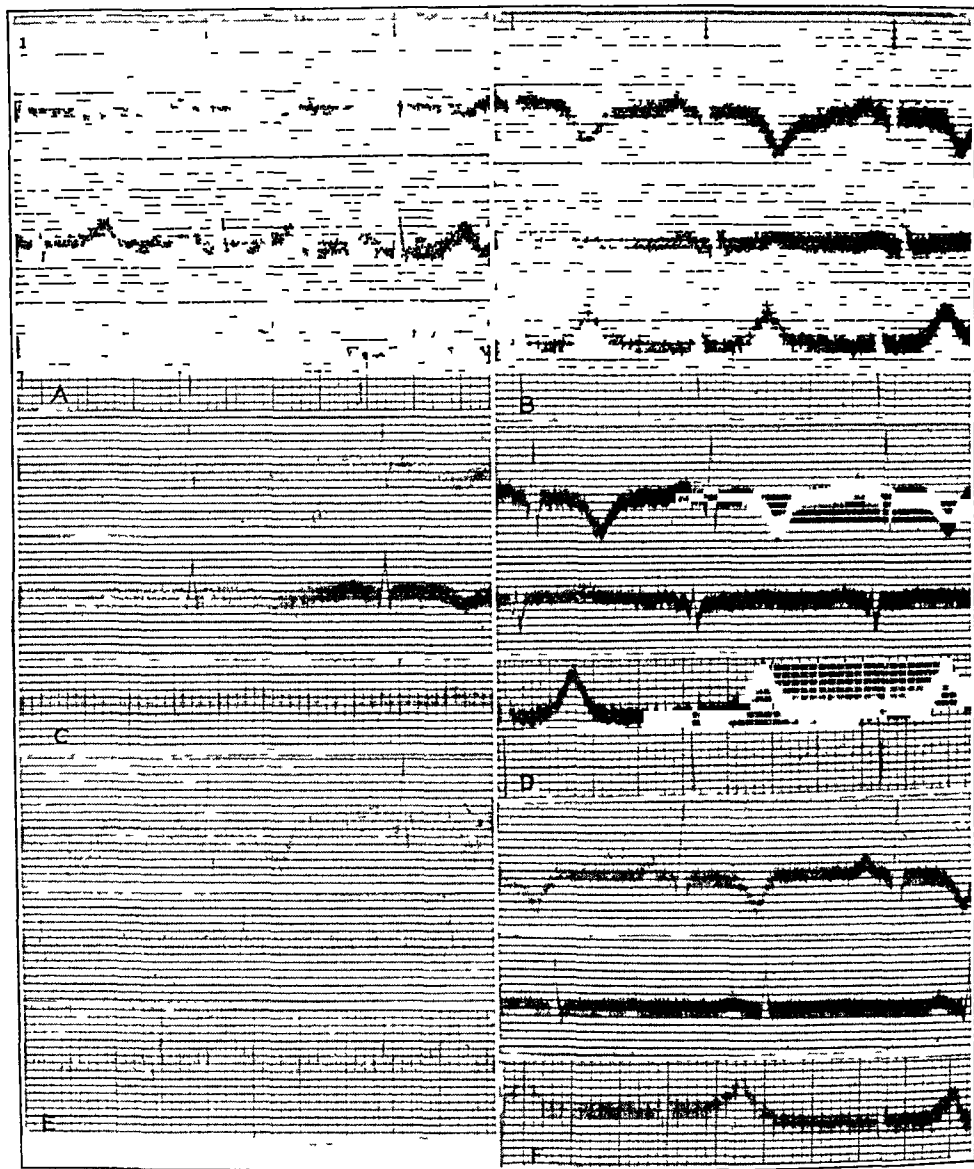


Fig 2 (Case 2)—*a*, this curve was taken six hours after the onset of a severe attack of precordial distress. The pain lasted about twenty-four hours. The T-wave is slightly negative in lead I and positive in leads II and III, *b* curve taken at 9:30 the following morning. There has been a definite change in the T-deflection in leads I and II. In the former it is more negative, in the latter it is almost iso-electric, *c*, taken at 2:30 p. m. of the same day. The T-wave has changed to a negative phase in lead II and is less positive in lead III. There is in addition a definite decrease in the amplitude of the QRS group, *d*, taken on the third day following the cardiac accident. The T-waves are similar to those shown in *b*. The S-wave in lead II has become more prominent than the R-peak. There has been marked increase in the amplitude of the S-deflection in the third lead, *e*, taken on the fourth day after onset of pain. The T-deflection is similar to that in *d*. The chief ventricular deflection in lead II has changed to a positive phase and the S-wave in lead III is less prominent, *f*, taken on the fifth day, similar to *c*.

vomiting. At the time the patient entered the hospital he was very weak, short of breath on the slightest exertion and still complained of pain in the chest. The lips were slightly cyanotic. The left cardiac dullness was just inside the anterior axillary line. The heart rate was 130 a minute with a pulse deficit of 40. The rhythm was irregular. The cardiac tones were indistinct. No murmurs were detected. There was, however, a friction rub over the lower cardiac area. Moist râles were heard in the bases of the lungs. The liver was palpable and slightly tender. The systolic blood pressure was 110 and later 90, and the diastolic pressure was 55. The diagnosis of coronary

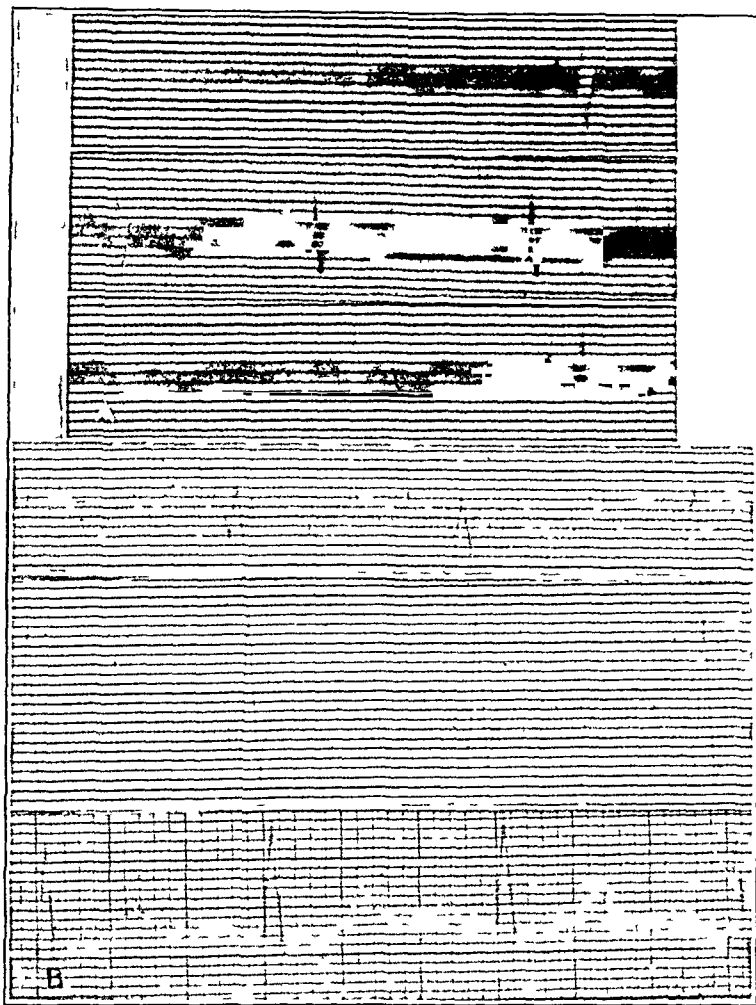


Fig 5 (Case 5)—*a*, electrocardiogram taken three weeks after a severe attack of precordial pain which lasted for about twelve hours and was associated with great difficulty in breathing. The T-wave is sharply negative in lead I, *b*, taken six months later. The T-deflection now is practically isoelectric in lead I, *c*, curve taken four weeks after prolonged attack of severe cardiac distress. This patient died in a few weeks from cardiac failure. The T-wave is a sharp downward deflection in lead I. This feature is less marked in lead II, while in lead III the T-wave is positive.

thrombosis was made. The course was slowly progressively downward, and the patient died from cardiac failure on Aug 15, 1922. At necropsy the descending branch of the left coronary was occluded. There was a large

whereas it had previously varied from 140 to 160. The patient remained in the hospital for almost five months. During most of this time his heart was in a critical condition. He had a persistently rapid cardiac rate. There was a gallop rhythm. He had frequent periods of cardiac irregularity, and at one time had an attack of rapid regular heart action which lasted for several hours. The patient was finally discharged April 2, 1922. He was at this time able to be up and was permitted to take a little exercise.

The first electrocardiogram (Fig 4 *a*) was taken two days after the patient entered the hospital. The ventricular deflections were very low in each lead. Five weeks later the amplitude of the QRS group (Fig 4, *b*) had increased and the S-deflection in lead III was most prominent. The T-wave is iso-electric in the three leads. The curve (Fig 4, *c*) taken in October, 1922, showed a left ventricular preponderance with a prominent R and S-deflection. The T-wave was iso-electric in lead I and positive in leads II and III.

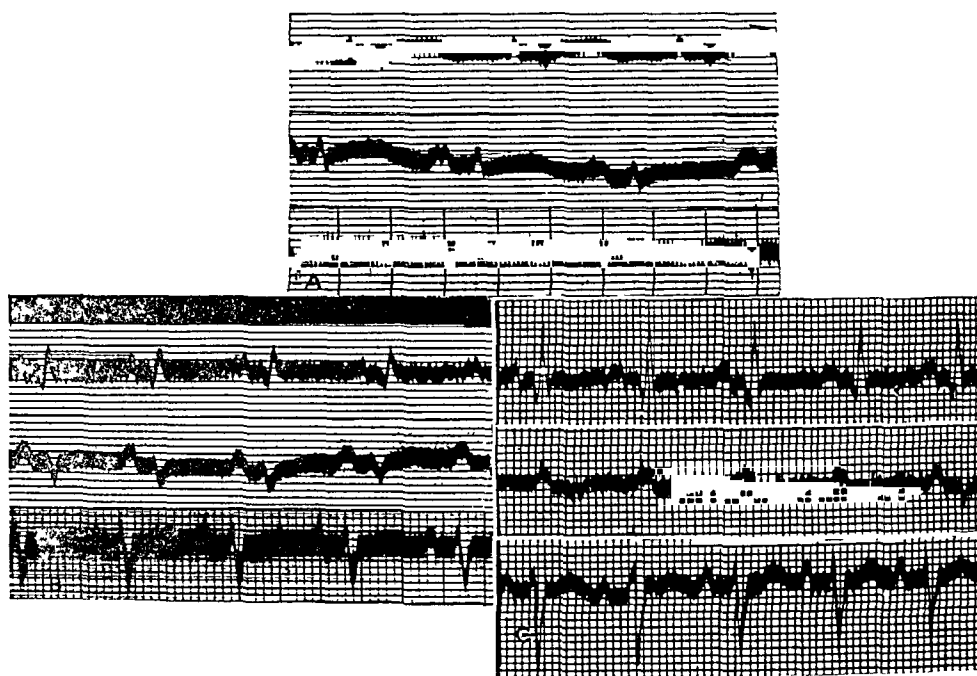


Fig 4 (Case 4)—*a*, curve taken twelve days after a sudden and severe cardiac upset. The amplitude of the QRS group is low in the three leads. The T-wave is slightly positive in leads I and II, *b*, taken thirty-three days following the first curve. The S-deflection in lead III has become much more prominent. The chief ventricular wave has remained low in leads I and II. The T-wave is practically iso-electric in the three derivations, *c*, taken eleven and one-half months after cardiac accident. The curve is that of left side preponderance. The T-wave is positive in leads II and III and iso-electric in lead I.

CASE 5—R S, aged 63, entered the Presbyterian Hospital on June 1, 1922, in the service of Drs Irons and Greer. He gave a history of having had a high blood pressure for ten years. His general health, however, had been fairly good during this time, and a few days prior to the onset of the present illness he had been doing fairly heavy physical work without discomfort. During the two days before entering the hospital he had had several attacks of precordial distress which were associated with weakness and shortness of breath. One of these attacks lasted about nine hours, during which the patient was very dyspneic and exhausted. One was accompanied by nausea and

Three of these patients consulted Dr Herrick one, two and five weeks respectively, following the attack. In each a probable diagnosis of coronary occlusion was made. The electrocardiogram showed changes in the T-wave. In the one in which the curve (Fig 5, *a*) was taken one week following the cardiac upset, the T-deflection was negative in the three leads. There was in addition a moderate decrease in the amplitude of the QRS group. The T-wave in the electrocardiogram (Fig 5, *b*) of the patient seen two weeks after the attack was sharply negative in lead I. In the curve of the third patient the final ventricular deflection was slightly negative in leads I and II.

One of these patients made a satisfactory recovery and was not short of breath on moderate exertion when seen by Dr Herrick. The other two had extensively damaged hearts. One was confined to bed for weeks because of cardiac failure. The other, at the time of the last report, had markedly impaired cardiac function.

The remaining three patients were followed in the outpatient department of Rush Medical College. They were first seen three, four and six weeks, respectively, following the cardiac accident. In two, the electrocardiogram showed changes in the T-deflection (Fig 6, *a*, *b* and *c*). In the third, there was a moderate decrease in the amplitude of the chief ventricular deflection and an increase in the duration of the QRS group. Each had signs and symptoms of cardiac failure when first seen. Two died within a few weeks following their first visit to the clinic. The third is now 65 years old and is in a fair state of health. He has, however, carefully obeyed instructions and has never exerted himself beyond the point where he begins to feel winded.

#### COMMENT

The electrocardiographic findings of eleven patients are presented. In one, the descending branch of the left coronary artery was ligated in the repair of a stab wound of the heart. In two, the clinical diagnosis of coronary thrombosis was verified at necropsy. In the remaining eight patients, the character and duration of the cardiac pain and the subsequent clinical course was as characteristic of coronary closure as in those in whom the diagnosis was checked by necropsy. It would thus seem that we were reasonably justified in making the diagnosis of coronary occlusion.

In eight of the eleven patients, the electrocardiograms showed changes in the T-deflection. In two, the T-wave was sharply negative in lead I, in four, in leads I and II, and in two, in each of the three derivations. In four, the electrocardiograms showed progressive changes in the final ventricular deflections. In the patient in whom the descending branch of the left coronary artery was closed by operation, the T-wave of the first electrocardiogram (Fig 1 *a*) was negative

partially healed infarcted area in the apical region of the left ventricle with a parietal aneurysm. An electrocardiogram taken two weeks before death showed a decrease in the amplitude of the QRS group. The T-deflection was isoelectric in the three leads.

The important features of the histories of the remaining six patients were essentially the same. Each recovered from a severe attack of precordial pain which lasted from eight to twelve hours. The pain

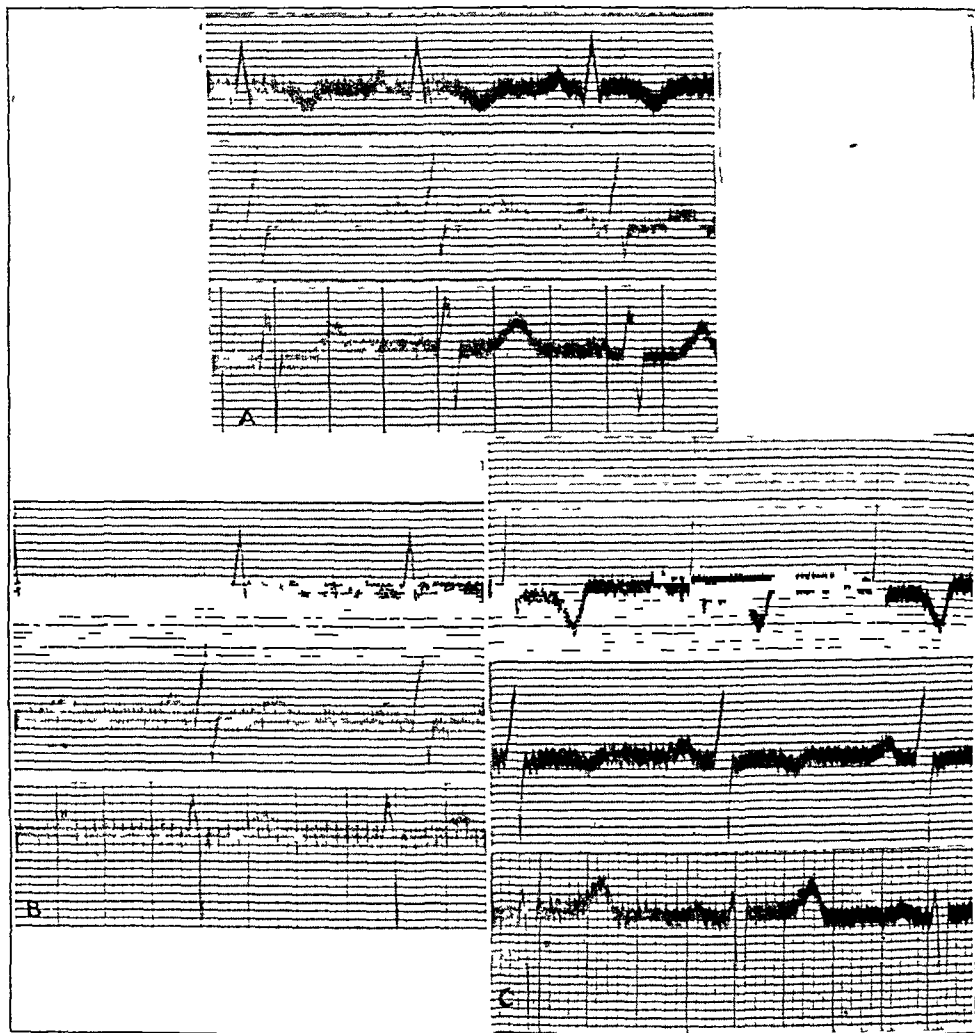


Fig 6—*a*, curve taken two weeks after an attack of precordial pain which lasted for about twelve hours and was not completely relieved by morphin. The T-wave is negative in each of the three leads and the amplitude of the chief ventricular deflection is moderately low, *b*, electrocardiogram taken one week following a severe attack of angina-like pain. The T-deflection in lead I is negative.

was referred to the arms and in some to the neck and was so severe that it was not entirely relieved by morphin. In all instances, the distress was associated with symptoms and signs of cardiac failure.

the final ventricular deflection following coronary occlusion is due to a change in the refractory period of a localized area of the left ventricle

In the experimental animal, the extent to which the T-wave became a negative phase seemed to depend on the size of the area of infarction. The latter in turn is dependent on the size of the vessel occluded and the degree of collateral circulation established. The collateral circulation between the various branches of the left coronary arteries varies markedly in the dog. A corresponding variation in this respect may be expected in man. The changes in the T-deflection following coronary closure may also be influenced further by the development of inter-ventricular conduction defect. This was noted in the dog and has been observed further in man.

A marked decrease in the amplitude of the QRS group following a prolonged period of precordial pain fully justifies the diagnosis of a serious cardiac accident. This type of electrocardiogram was associated with extensive myocardial change in the dog and followed the closure of the circumflex branch of the left coronary artery in all instances in which the animal survived the operation. The patient reported by Dr. Herrick and one in our series who showed the foregoing electrocardiographic findings, came to necropsy. In each instance branches of the circumflex were occluded along with that of the descending branch of the left coronary artery. The other patient in our series had a severe and damaged heart. He was in the hospital for more than five months, and is again in a serious condition.

#### CONCLUSIONS

Experimental and clinical observations justify the belief that the electrocardiograph may be employed to advantage in the diagnosis of coronary thrombosis in man. It is predicted that a large percentage of those who have an occlusion of the left coronary artery will show significant changes in the electrocardiogram within the first few days following the cardiac accident. In some instances, the alteration in the electrocardiogram may persist for weeks. Changes in the T-deflection and a decrease in the amplitude of the QRS group are the most constant findings. The former is apparently dependent on the formation of an area of infarction in the apical region of the left ventricle. The latter has been associated with more extensive and disseminated changes in the myocardium.

in each of the three leads. In later curves (Fig 1, *b* and *c*), this wave became less negative and finally changed to a positive deflection (Fig 1, *d*). The most striking alteration in the T-wave (Fig 2, *a* and *f*) was noted in the second patient in whom the first curve was taken on the same day as the cardiac accident and daily thereafter during the period of hospitalization. One of the patients studied by Robinson and Hermann showed similar progressive changes in the electrocardiogram. The variations in the T-wave of the electrocardiogram (Fig 3, *a* and *c*) of the third patient was definite but less characteristic.

In six patients, there was a decrease in the amplitude of the QRS group. In two, the amplitude was low (Fig 3, *c* and Fig 4, *a*). In one of these, the low deflection was noted in the first curve taken thirteen days after the onset of the cardiac accident. Nine months later, the heights of the QRS deflection had returned to normal (Fig 4, *c*). In the other, the reduction in amplitude occurred some time between the third and fourteenth day after the coronary closure. In another instance, the change in height<sup>9</sup> of the deflection was transient and noted first on the second day (Fig 2, *c*). One patient had moderate reduction in amplitude of the initial ventricular waves in the record taken one week after the attack of cardiac pain (Fig 5, *a*).

The foregoing changes in the T-wave and the amplitude of the QRS group resemble closely those in the dog following the ligation of the branches of the left coronary artery. These changes were most striking, and the resemblance to those of the dog were greatest in those patients in whom curves were taken early and at frequent intervals subsequent to the coronary accident. This is to be expected since the greatest changes occur in the heart during the first few days after the coronary closure. Curves taken at a later date may thus fail to show characteristic changes. This perhaps accounts for the negative findings in some of the cases which have been reported.

The negative T-deflection is the most constant and characteristic electrocardiographic findings following coronary closure. It is to be noted that the peak of this deflection is sharp. This feature persists throughout the change from negative to iso-electric phase and resembles closely the alteration in the T-wave produced experimentally by Wilson and Herrmann<sup>9</sup> by varying the degree of block of the right branch of the auriculoventricular bundle. The same type of T-wave may also be produced by changing the refractory period of the apical region of the left ventricle by cooling. It is not improbable that the alteration in

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<sup>9</sup> Wilson and Hermann. An Experimental Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of Dog, *Heart* 8 229, 1921

definite increase of their heart shadow on the roentgenograms. The method we employed was as follows, for the first eleven rabbits we injected 25 mg of spartein sulphate dissolved in 0.4 to 0.5 cc of distilled water, followed in from seven to ten minutes by 0.1 cc of epinephrin chlorid, for the remaining five rabbits we used an amount of spartein sulphate equivalent to 12 mg per kilogram of body weight, followed by 0.1 to 0.15 cc of epinephrin chlorid. All injections were made intravenously into an ear vein. The spartein sulphate employed was put up by Merck & Co., and the epinephrin chlorid was the 1:1000 solution prepared by Parke, Davis & Co. Care was used to have the epinephrin chlorid always in a freshly prepared solution. The injections were repeated weekly until a definite and permanent increase in the size of the heart had occurred, at which time the effect of intravenous injection of crystalline strophanthin was studied. The strophanthin used was a 1:1,000 solution prepared in ampules by Merck & Co. It was tested by us by the Hatcher method and found to have a rabbit unit (minimum lethal dose per kilogram) of 0.6 mg (0.6 cc). The amount of strophanthin given in this study was 30 per cent of this rabbit unit. This should approximate the therapeutic dose, as Levine<sup>6</sup> has shown that the toxic effect occurs when about 50 per cent of the minimum lethal dose has been given, and the therapeutic dose should be somewhat less. This amount (30 per cent) is about the equivalent of the dose used clinically. After the strophanthin, roentgenograms were taken at five, ten and fifteen minute intervals, the heart shadow showing the greatest change when compared with the roentgenogram taken just before the injection was chosen. Roentgen-ray films were obtained with the tube at a distance of 5 feet (152 cm), using a current of 30 milliamperes backed up by a 4½ inch (11.4 cm) spark gap with an exposure of seven seconds. This greatest change usually occurred after ten minutes, although in a few instances it was seen on the five or on the fifteen minute plate. To determine changes in size, the heart was outlined in pencil on the film, and this outline was traced on smooth white paper of uniform texture. The silhouettes were cut out and weighed, the weights being accurate to 0.1 milligram. We believe this to be more exact than other methods for comparing the size of heart shadows. This method was formerly used by Dr. A. E. Cohn. No changes were considered significant unless they were greater than 10 per cent.

#### EXPERIMENTAL WORK

As all of these experiments were conducted on the same plan, a summary of but one case will be included as an example.

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<sup>6</sup> Levine, S. A. J. Exper. M. **29** 485, 1919



# STUDIES ON THE RABBIT'S HEART<sup>1</sup>

## I EFFECT OF STROPHANTHIN ON THE SIZE OF THE NORMAL AND OF THE ABNORMAL HEART

G F STRONG, M D

VANCOUVER, B C

AND

BURGESS GORDON, M D

SPOKANE, WASH

Clinical studies on the changes in the size of the heart are frequently difficult to control. A patient with cardiac decompensation lends himself poorly to the manipulation necessary for roentgen-ray studies, and furthermore, fluid in the chest frequently renders accurate measurements of the heart difficult. There are, therefore, few exact studies on the changes in the size of the decompensated heart that may occur in response to treatment, neither has the experimental study of this problem been sufficiently investigated. It is generally recognized, following the work of Fleischer and Loeb<sup>1</sup> and Walker,<sup>2</sup> that a chronic myocarditis can be produced in rabbits by the repeated injection of spartein sulphate and epinephrin chlorid. Fraser<sup>3</sup> further showed that a permanent enlargement followed repeated injections of these drugs. It occurred to us that this offered a means of studying the effect of various measures on the damaged heart, and the study of the effect of strophanthin was therefore undertaken. Vaquez and Dimitrakoff<sup>4</sup> are of the opinion that strophanthin (ouabain) intravenously caused a definite decrease in the size of the decompensated heart. Their work has been entirely clinical and as such is somewhat difficult to control. We hoped to investigate the problem experimentally.

We have attempted to produce a chronic myocarditis in rabbits by means of repeated injections of spartein sulphate and epinephrin chlorid,<sup>5</sup> and have followed the changes in size by roentgen-ray studies. Sixteen rabbits were injected, seven of which died before any marked change had occurred, of the remaining nine rabbits, six have shown

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\*From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine of the Harvard Medical School.

1 Fleischer, M S, and Loeb, L. Experimental Myocarditis, *Arch Int Med* 3 78 (Feb) 1909.

2 Christian, H A, Smith, R M, and Walker, I C. Experimental Cardiorenal Disease, *Arch Int Med* 8 469 (Oct) 1911.

3 Fraser, F R. *J Exper M* 22 292, 1915.

4 Dimitrakoff. These, Paris, 1922.

5 Footnote 1, 2 and 3.

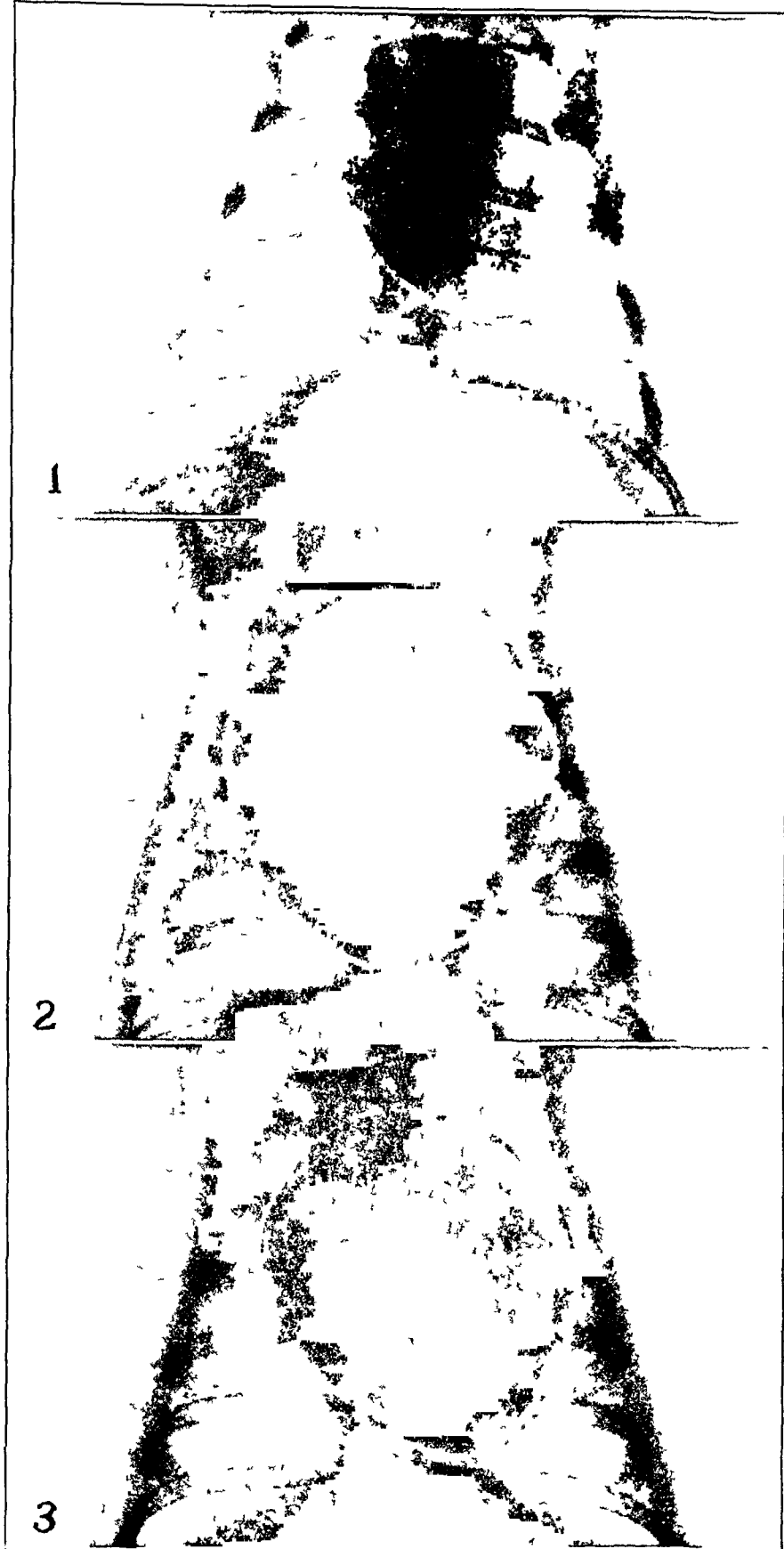


Fig 1 (Rabbit 14)—Roentgenogram taken Jan 9, 1923 The weight of heart silhouette was 609 mg

Fig 2 (Rabbit 14)—Roentgenogram taken March 2, 1923 The weight of the heart silhouette 1058, a 75 per cent increase over Fig 1

Fig 3 (Rabbit 14)—Roentgenogram taken March 2, 1923, ten minutes after a 0.43 cc 1,000 strophanthin solution given intravenously There was a decrease of 13 per cent in size

Rabbit 14, weighing 27 kg, whose heart silhouette weighed 60.9 mg (Fig 1), was given weekly intravenous injections of spartein sulphate, 32 mg (dissolved in 0.4 to 0.5 cc distilled water), followed in seven to ten minutes by 0.1 cc of epinephrin chlorid solution intravenously. From a roentgenogram taken on February 20, after five such injections, we obtained a silhouette weighing 85 mg, an increase of 39 per cent over the original weight. On this day an intravenous injection of strophanthin (25 per cent of the rabbit unit in this instance) caused a decrease in the size of the heart of 13 per cent. On March 2, after six injections of spartein sulphate and epinephrin, a roentgenogram (Fig 2) showed a heart of such size that the silhouette weighed 105.8 mg, an increase of 75 per cent over the original weight. Strophanthin

TABLE 1—*Sparteinsed Hearts with Definite Dilatation*

Experi- ment Num- ber	Rabbit Num- ber	Weight of Heart Silhouette In Milligrams at Beginning of Experiment	Number of Injections of Sparteins and Epine- phrin*	Percentage of Increase in Weight of Heart Silhouette Following Sparteins and Epinephrin	Amount of Stro- phanthin in C c †	Weight of Heart Silhouette Imme- diately Before Stro- phanthin	Weight of Heart Silhouette Imme- diately After Stro- phanthin	Per centage of Decrease Due to Stro- phanthin
1	14	60.9	5	39	0.36	85.0	74.0	13
2	15	75.6	5	10	0.43	81.8	75.4	8
3	3	57.6	4	23	0.22#	70.8	62.4	12
4	2	80.2	9	13	0.45	90.8	85.4	6
5	3	57.6	9	17	0.48	67.2	59.8	11
6	14	60.9	6	75	0.43	105.8	91.4	14
7	15	73.6	6	23	0.52	90.5	74.8	17
8	2	80.2	9	18	0.45	94.6	84.4	11
9	3	57.6	9	20	0.48	69.0	57.0	17
10	17	87.4	5	19	0.68	94.0†	106.9	14§
11	16	67.2	6	14	0.43	76.6	68.8	10
12	14	60.9	6	83	0.43	111.6	97.2	13
13	17	87.4	6	27	0.68	111.2	106.4	4
14	16	67.2	6	18	0.43	78.2	70.4	10

In these tables the following symbols are used with the meaning indicated

\* Given at approximately weekly intervals

† The amount of strophanthin used was 0.18 cc per kilogram. This equals 30 per cent of the rabbit unit

# Arnaud's ouabaine

‡ After exercise to exhaustion. Heart possibly contracted

† Twenty per cent of rabbit unit

§ Increase

given intravenously on March 2 caused a decrease in size of 13 per cent (Fig 3). On March 6, the silhouette weighed 111.6 mg, an increase of 83 per cent. Strophanthin again caused a decrease of 13 per cent. It is remarkable, but probably not significant, that in this rabbit the strophanthin in each instance caused a decrease of 13 per cent in the size of the heart. Electrocardiograms on March 7 showed the same form of curve as that obtained on January 8.

The accompanying tables give in detail the results obtained on intravenous injection of crystalline strophanthin.

The first table shows those cases in which a definite myocarditis had been produced, as evidenced by cardiac enlargement. In these cases there was a uniform response to the injection of strophanthin. The decrease

the first roentgenogram was taken. Then the strophanthin was injected and the five, ten, and fifteen minute plates were obtained. At no time after the strophanthin had been injected was the rabbit disturbed, except to insert new films under the back and to correct any faulty position. We feel that physical exertion has been effectively ruled out as the cause for decrease in the size of the heart. The possibility that an emotional influence might be responsible occurred to us. We therefore injected normal saline intravenously into two rabbits, using the same amount of fluid as was given in the strophanthin injections, and making all other details in the experiments identical. The hearts did not change appreciably in size, there was only a slight increase in one case and a slight decrease in the other case in the weight of the heart silhouettes after the saline. The changes were so small, 38 and 30 mg, respectively, that they are quite within the limit of error. It occurred to us to study the effect of spartein sulphate and epinephrin

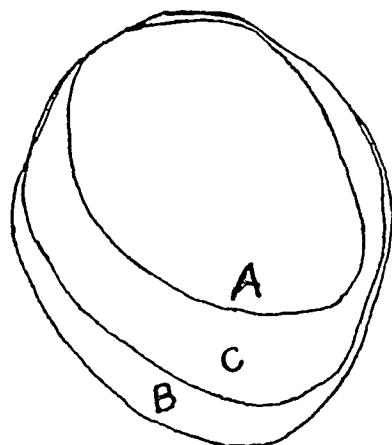


Fig 4 (Rabbit 14)—Heart outlines superimposed for comparison. *A* is the outline of the heart in Fig 1, showing the size at the beginning of the experiment. *B* is the outline of the heart in Fig 2, showing the increase due to six injections of spartein and epinephrin. *C* is the outline of the heart after one injection of strophanthin.

chlorid when given during the routine treatments. The spartein sulphate had no effect on the size of the heart in three cases in which it was studied. This may be taken as added evidence that an emotional influence is not the cause of the decrease after the strophanthin. In five cases, the effect of epinephrin chlorid when injected in 0.1 cc amounts intravenously was observed. In each case there was an increase in the size of the heart, in three of the cases this increase was over 20 per cent. This increase following epinephrin came on earlier than the strophanthin effect and did not last so long. We feel that with these methods of controlling our results there can be little doubt that the decrease in size of the heart recorded in our tables is due to the effect of strophanthin on the heart muscle.

ranged from 4 to 17 per cent, with an average of 10 per cent. In one case (Experiment 10) there was an increase after injection of strophanthin. This rabbit had been exercised to exhaustion six hours previous to this experiment, and its heart may still have been somewhat contracted. Acute overexertion does cause definite decrease in the heart, as will be reported by us in another article.<sup>7</sup> This usually disappears in two hours. It may have persisted longer in this case. Subsequent injection of strophanthin caused a slight decrease in size in this case (Experiment 13). In these experiments we waited at least four full days after giving an injection of strophanthin before repeating it, so that no part of the first dose remained at the time the second dose was given.

TABLE 2—*A, Normal Hearts*

Experi- ment Num- ber	Rabbit Num- ber	Weight of Heart Silhouette in Milligrams at Beginning of Experiment	Number of Injections of Sparte- in and Epine- phrin*	Percentage of Increase in Weight of Heart Silhouette Following Sparte- in and Epinephrin	Amount of Stro- phanthin in C c †	Weight of Heart Silhouette imme- diately Before Stro- phanthin	Weight of Heart Silhouette imme- diately After Stro- phanthin	Per- centage of Decrease Due to Stro- phanthin
15	19	61.6	0	0	0.21#	61.6	62.4	1%
16	20	61.1	0	0	0.48	61.1	66.0	8%
17	21	81.0	0	0	0.52	81.0	77.2	5%
18	22	70.0	0	0	0.43	70.0	76.0	8%
19	19	61.6	0	0	0.48	53.4	50.8	13%
20	7	63.2	0	0	0.43	71.2	53.6	25%
21	8	61.6	0	0	0.36	48.6	67.0	38%
<i>B, Sparteinized Hearts with No Dilatation</i>								
22	9	71.0	4	0	0.22#	72.4	70.4	3%
23	9	71.0	9	0	0.50	70.4	64.8	8%
24	10	70.3	9	0	0.45	66.2	73.0	10%
25	11	65.4	8	0	0.28#	61.0	51.0	18%
26	18	76.0	5	0	0.50	60.4	64.0	6%
27	9	71.0	9	0	0.50	72.2	63.0	13%
28	10	70.3	9	0	0.45	66.2	58.8	11%

In the second table are shown the results of strophanthin on normal hearts. Of these fourteen experiments, seven were performed on normal rabbits and the other seven on rabbits that had received injections of spartein and epinephrin but had shown no cardiac enlargement. These experiments show less constant results than in the case of the animals with dilated hearts. The average decrease in size was only 2 per cent as compared with 10 per cent for rabbits with chronic myocarditis.

The question is immediately raised, Is the decrease in size due to the strophanthin or to other factors? We know that physical exertion does decrease the size of the rabbit's heart. Care was used in putting the rabbit on the animal board so that it exerted itself as little as possible, and it was left absolutely quiet for two or three minutes before

<sup>7</sup> Reported in Studies of Rabbit Heart II. "Effect of Vigorous Exercise on Size of Normal and Abnormal Rabbit Heart."

# STUDIES ON THE RABBIT'S HEART <sup>†</sup>

## II EFFECT OF VIGOROUS EXERCISE ON THE SIZE OF THE NORMAL AND THE ABNORMAL HEART

BURGESS GORDON, M D

SPOKANE, WASH

AND

G F STRONG, M D

VANCOUVER, B C

By means of roentgen-ray studies and physical examination, certain observations have been reported on the effect of exertion on the size of the heart. We have been unable, however, to discover any reference to roentgen-ray studies on the hearts of animals subjected to vigorous exercise. Secher,<sup>1</sup> in 1921, reported some investigations on wild rats in which a group of eleven had been run until they died from the effects of exercise. From his observations, which consisted in measuring the hearts after death, he concluded that acute over-exertion produced dilatation of the heart. Boigey<sup>2</sup> reported orthodiagraphic studies on competitors before and after a 42 kilometer Marathon race in which there was dilatation of the heart. In the same paper, he observed that contraction of the heart followed a 100 meter foot race. Dedichen<sup>3</sup> examined 226 participants before and after a 50 kilometer Marathon by means of palpation and percussion, but was unable to demonstrate any cardiac enlargement. The impression has been general that the first response to exercise was a decrease in size, followed after further exertion by a moderate dilatation.

In our studies, we selected a group of healthy rabbits which had been confined for some time in small animal cages. A group of "sparteinized" rabbits, reared under similar conditions, was also studied. These animals had received weekly intravenous injections of 25 mg of spartein sulphate dissolved in distilled water, followed in from seven to ten minutes by 0.1 c.c. of a 1:1,000 solution of epinephrin chloride. This technic was a modification of the procedures recommended by Walker<sup>4</sup> for producing a chronic myocarditis. These will be referred to as "sparteinized" rabbits. When there was definite enlargement of the heart, as evidenced by roentgen-ray films, the rabbits were considered to have a chronic myocarditis, the histologic findings of which

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1 Secher, K. *Hospitalstidende* **64** 49, 1921, No. 5, p. 65

2 Boigey. *Presse med* **26** 657, 1921

3 Dedichen. *Acta Med Scand* **53** 738, 1921

4 Christian, H. A., Smith, R. M., and Walker, I. C. *Experimental Cardio-renal Disease*, *Arch Int Med* **8** (Oct) 1911

The postmortem examination of the rabbits studied revealed changes similar to those described by Walker<sup>2</sup> The histologic changes were the production of cellular foci made up of lymphoid, plasma and young connective tissue cells, around necrosed or severely damaged muscle fibers, and the proliferation of connective tissue, sometimes quite extensive, replacing muscle fibers and extending into and separating the damaged muscle cells The exact histologic picture varied with the age of the lesion, in the long standing cases a more extensive scar formation occurred

This method of investigation, studying the responses of definitely damaged heart muscle to various procedures, offers, we believe, further possibilities We hope to follow some rabbits with an experimentally produced myocarditis for a long period of time and to report subsequently on our findings

#### CONCLUSIONS

- 1 Strophanthin given intravenously in doses comparable to those used clinically causes a definite decrease in size of the rabbit's heart

- 2 This decrease is most marked in cases of experimentally produced myocarditis, as evidenced by cardiac dilatation It also occurs to a certain extent in normal rabbits

- 3 The heart usually begins to return to normal size at the end of fifteen minutes and always recovers completely after two hours

have been seen in animals that have died or were killed during the course of the injections. The changes are those described by Walker.<sup>4</sup> Sixteen rabbits received such injections, nine of which were living when this study was undertaken. In three of the latter animals there was no evidence of cardiac enlargement.

The method we employed to exercise the rabbits to exhaustion was as follows. A squirrel-cage, treadmill type, a cylinder 4 feet (121.5 cm) in diameter and 16 inches (40.64 cm) in width, was constructed with smooth wooden sides and heavy wire-screen runway. This cage was operated by means of a simple crank. The outline plan consisted, first, in taking a roentgen-ray film<sup>5</sup> of the thorax while the rabbit was fastened on its back to the animal board. The rabbit was then placed in the treadmill which was revolved at a speed corresponding to the progress of the animal. The revolutions necessary to produce exhaustion averaged about twenty-two in number, and the procedure occupied

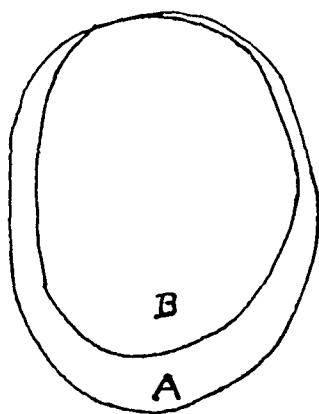


Fig 3 (Rabbit 16)—Heart outlines superimposed for comparison. *A* is the outline of the heart in Figure 1. *B* is the outline of the heart in Figure 2, and shows the decrease due to exercise.

approximately three minutes. The animal was not removed until it showed evidence of marked exhaustion. It not only became limp, cyanotic (shown in the ears), markedly dyspneic, and unable to support itself, but it failed to react to ordinary stimuli, although, as pointed out later, the rabbits recuperated promptly and completely. Another roentgen-ray film was obtained as soon as the animal could be returned to the board. In a few cases we followed the recovery of the heart by frequent roentgen-ray plates. The heart shadow was outlined on the film with pencil, and a silhouette was traced from this on smooth white paper. This silhouette was carefully cut and weighed, the weight being accurate to 0.1 mg.

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<sup>5</sup> The film was taken with the tube at a distance of 5 feet (152 cm), using a current of 30 milliamperes backed up by a 4½ inch (11.4 cm) spark gap with an exposure of seven seconds.



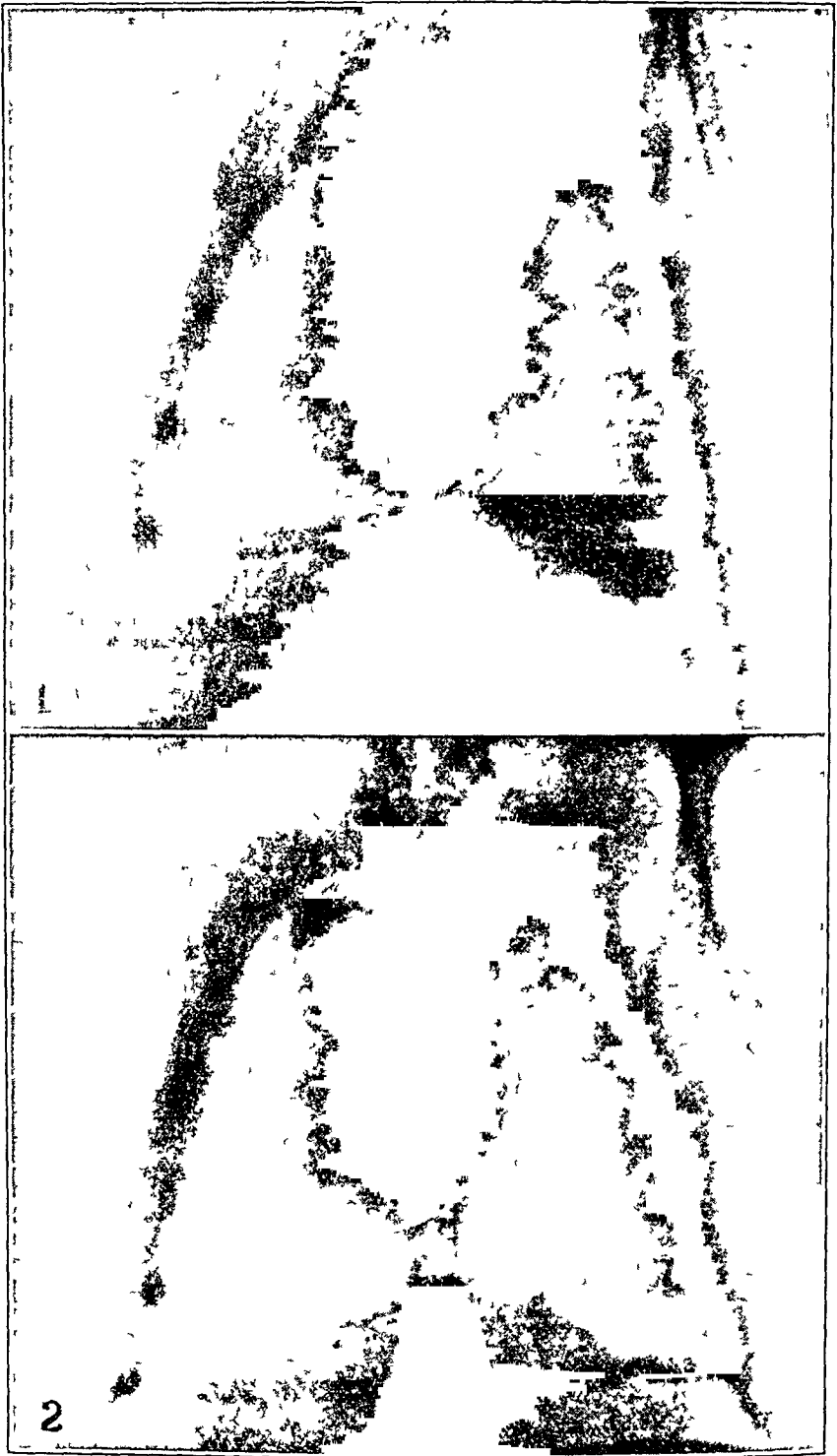


Fig 1 (Rabbit 16) —March 3, 1923, before exercise The silhouette in this case showed an increase in weight of 20 per cent over the weight of the silhouette made from the first roentgenogram of this animal on Jan 11, 1923

Fig 2 (Rabbit 16) —March 3, 1923, showing a decrease in heart size of 28 per cent after exercise

effects from this overexertion (some of these rabbits have been under observation for two months following our first experiments) This was unexpected in the case of those rabbits with marked cardiac enlargement, due to a definitely damaged myocardium We rather expected dilatation or at least no contraction in these animals after exercise It would seem that these results emphasize the relative unimportance of merely objective findings in heart disease Although these rabbits had one objective sign of an impaired heart, i e, an enlargement, they apparently had sufficient cardiac reserve to enable them to respond to this acute overexertion in a normal way Two of the animals with a definite myocarditis were exercised to exhaustion on March 7 Three hours later, when the hearts had returned to their normal size, the experiment was repeated and the response was the same

#### CONCLUSIONS

- 1 Normal rabbits were exercised to complete physical exhaustion
- 2 The result in every instance was a definite decrease in the size of the heart
- 3 Six animals in which experimental myocarditis had been produced responded to overexertion in a similar manner
- 4 Although the rabbits had been observed for only a comparatively short time, there was no evidence that acute overexertion influenced the general condition of the animals

By reference to the table, it will be observed that all rabbits, both in the normal and in the two "sparteinized" groups, showed definite contraction of the heart. Two apparent exceptions (Experiments 2 and 3) occurred in which the animals failed to exercise properly. These animals subsequently showed definite contraction (Experiments 8 and 18). The average decrease of all cases was about 19 per cent, which is too large to be due to any possible error in our method of estimating changes in the size of the heart. From the table, it is apparent that there is no difference in the response to overexertion between the sparteinized animals showing increased heart size and those without

*Effect of Exercise to Exhaustion on the Size of the Heart\**

Experi- ment Number	Rabbit Number	Date	Percentage Increase in Weight of Heart Silhouette After Spartein and Epinephrin	Weight of Silhouette Before	Weight of Silhouette After	Per Cent Decrease in Size
A Normal Hearts						
1	7	1/13		58.0	49.6	14
2	8	1/13		52.2	55.4	5*Incr
3	17	1/13		87.4	87.4	0*
4	18	1/13		76.0	60.0	21
5	19	3/3		56.2	48.7	13
6	20	3/3		62.6	52.6	15
7	21	3/3		81.4	67.0	17
8	7	3/3		64.8	54.0	16
9	8	3/3		53.0	37.2	29
B Sparteinized Hearts Showing No Dilatation						
10	2	1/13		77.2	56.6	26
11	3	1/13		60.3	48.4	20
12	9	1/13		72.0	60.0	16
13	10	1/13		69.2	56.4	18
14	18	3/3		77.6	60.6	22
15	9	3/3		67.2	57.2	15
16	10	3/3		64.0	51.8	19
C Sparteinized Hearts Showing Dilatation						
17	16	3/3	20	80.8	58.0	28
18	17	3/3	19	104.0	75.2	27
19	2	3/7	15	92.2	74.2	19
20	3	5/7	13	65.0	54.4	16
21	15	3/7	7	78.0	60.0	23
22	14	3/7	44	88.2	78.8	10
23	2	3/7	17	93.8	74.8	20
24	3	3/7	11	64.2	56.2	12

\* These animals failed to exercise properly. In subsequent experiments the results were better.

enlargement. In part C of the table, the fourth column from the left shows the amount of cardiac enlargement present when these experiments were performed, as judged by the percentage increase in weight of the heart silhouette. In those instances in which roentgenograms were repeated at intervals after exercise, there was observed a gradual return of the heart to normal size. Within two hours, this return was complete.

Following the exercise, the rabbit itself made a surprisingly quick recovery, and although it took two hours for the heart to return to normal size, the rabbit was apparently quite recovered in fifteen minutes. It was surprising that these animals suffered no obvious ill

authors considered the infection rare Stiles<sup>3</sup> reported the first American case in 1902 Following this, Allen<sup>4</sup> and Emerson<sup>5</sup> each reported one case From various sections of the United States reports of cases have been made by Logan and Sanford,<sup>6</sup> McNeil,<sup>7</sup> Smithies,<sup>8</sup> Hemmeter,<sup>9</sup> Lyon,<sup>10</sup> Simon<sup>11</sup> and McGill<sup>12</sup> Most of the cases were detected by stool examinations and many of them were associated with a diarrheal condition Kofoed<sup>13</sup> found this flagellate in about 6 per cent of 1,500 apparently healthy recruits coming from all sections of the United States Maxcy<sup>14</sup> reports that *Giardia* infection is much more common in children than in adults The infection has also been reported from most of the continental countries

#### THE ORGANISM

An excellent and detailed description of this flagellate has recently been given by Simon<sup>15</sup> Its appearance is quite characteristic In brief, it may be described as a silvery colored body, from 10 to 20 microns in length and from 5 to 12 microns in width In shape it resembles a pear split into two parts along the long axis On the anterior half of the flat surface there is a cuplike depression, the sucking disk, or peristoma which is best seen in a lateral view There are two nuclei anteriorly, which give the organism, when viewed on the flat surface, a conical, facelike appearance similar to that of a skate fish There are eight flagella arranged in pairs By means of the peristoma they attach themselves by suction to the epithelial cells

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3 Stiles, C W First American Case of Infection with *Lambli*a Duodenalis, Washington M Ann **1** 64 (March) 1902

4 Allen, W A Case of *Lambli*a Intestinalis, Old Dominion J M & S **10** 417 (June) 1910

5 Emerson Clinical Diagnosis, Ed 3, Philadelphia, J B Lippincott Co, 1911

6 Logan, A H, and Sanford, A H The Significance of *Lambli*a Intestinalis in Stool Examination, J Lab Clin Med **2** 618 (June) 1917

7 McNeil, H L Flagellate Infection of Intestines, Southern M J **10** 544 (July) 1917

8 Smithies, Frank The Frequency of Protozoic Enterocolitis in the Middle West, Am J M Sc **156** 173 (Aug) 1918

9 Hemmeter, J C Clinical Notes on an Intestinal Infection with *Giardia* Duodenalis, Tr Am Gastro-enterological Assn, 1920

10 Lyon, B B V Chronic Arthritis with *Lambli*iasis, M Clinics N A **4** 1153 (Jan) 1921

11 Simon, S K *Lambli*a Intestinalis Infestation and Its Treatment, Southern M J **15** 458 (June) 1922

12 McGill, C *Giardiasis*, J A M A **78** 179 (Jan 21) 1922

13 Kofoed, C A Intestinal Protozoan Infections in United States Army Troops, Tr Am Gastro-enterological Assn, 1919, p 262

14 Maxcy, K F *Giardia* (*Lambli*a) Intestinalis Common Protozoan Parasite of Children, Bull Johns Hopkins Hosp **32** 166 (May) 1921

15 Simon, C E *Giardia* Enterica a Parasitic Intestinal Flagellate of Man, Am J Hygiene **1** 440 (July) 1921

# GIARDIA INTESTINALIS INFECTION \*

EDWARD HOLLANDER, M D

NEW YORK

*Giardia (Lambia) intestinalis*, discovered by Lambl in 1859, for a long time was considered a nonpathogenic parasite. It was believed to be rare in temperate climates and was regarded as an organism of negligible importance. Increased interest in this flagellate was awakened during the Great War, as numerous cases of intractable diarrhea were reported which were believed to be caused by this parasite. The English and the French, especially, believed it to be the etiologic agent in many cases of "trench diarrhea." Since the parasite had received but scant attention in the past, many interesting problems regarding its geographic distribution, pathogenicity and treatment presented themselves.

*Giardia intestinalis* differs from the other protozoa that inhabit the human intestinal tract in that its habitat is the duodenum and jejunum. The vegetative forms are readily detected in the duodenal contents in many cases in which the stools contain few or none of the cysts. Within the past few years, since the introduction of the Meltzer-Lyon method of duodenobiliary drainage, which includes the microscopic examination of the duodenal contents, many human carriers of this infection are being brought to light in temperate zones. Previously, when the diagnosis was made by the stool examination alone, many of these cases would have passed unobserved.

During the past two and one-half years, in performing duodenobiliary drainage on 170 patients, nine cases of infection by *Giardia intestinalis* were found. Eight of these patients were natives of Russia and Austria, but they were residents of New York City for many years. The ninth patient was a native and resident of New York City. It was not possible in any of the cases to discover when or where the infection originated. None of the patients had ever been in tropical countries.

Previous to these cases there are only two reports of this parasite on record in New York state. The first report is by DuBois and Toro,<sup>1</sup> in 1912, who reported four cases in children, the other is by Chace and Tasker,<sup>2</sup> in 1917, who reported three cases in adults. These

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\* From the Medical Department, Mount Sinai Hospital.

1 DuBois, E. F., and Toro, W. C. Two Cases of Infection with *Lambia-Intestinalis*, Proc. N. Y. Path. Soc. **12** 32, 1912.

2 Chace, A. F., and Tasker, A. N. The Diagnosis and Treatment of the Flagellate Diarrhoeas, J. A. M. A. **68** 1528 (May 26) 1917.

forms of *Giardia* cannot infect man. He believes that the human infection is of human origin. However, it must be pointed out that Fantham and Porter experimented with virulent strains of the organism from human cases of dysentery. They found that the strain from Flanders was more virulent than that from Gallipoli. This difference in virulence might well explain the divergent results obtained by these workers. The organism has also been found in rabbits, dogs, guinea-pigs and sheep.

#### PATHOGENICITY

The pathogenicity of *Giardia intestinalis* has been the subject of much discussion. The earlier writers believed it to be nonpathogenic. Since the Great War, most authorities hold that while no symptoms are exhibited when the flagellates are few in number, they may become pathogenic when they are present in enormous numbers and cause an enteritis and diarrhea of moderate severity. Thus Porter,<sup>20</sup> in an enumerative study of the cysts of *Giardia intestinalis* in dysenteric feces, estimated that the number of cysts in a bulky infected stool exceeded 14,000,000,000, and in an infected stool of average volume, totaled 324,000,000. It was emphasized that each of these cysts was derived from a flagellate organism provided with a sucking disk whereby it abstracted its nourishment from the intestinal epithelial cells. Furthermore, Wenyon and O'Connor<sup>21</sup> point out that in diarrheal conditions, these cysts frequently occur enmeshed in large quantities of mucus which must be produced by the intestine at the site of the infection. Fantham and Porter<sup>18</sup> found that intestinal lesions can be produced in kittens and mice by the suckorial action of the flagellates.

Those authors that consider *Giardia intestinalis* as nonpathogenic base their opinion on the fact that the parasite may be found in healthy people. In the tropics, they are found in the stools of more than 25 per cent of apparently healthy persons after a saline purge. However, this same argument can be used to deny the causal relation of *Entamoeba histolytica* to a specific form of dysentery, since Hegner and Payne,<sup>22</sup> in a review of the protozoal infections, record a surprisingly high incidence of healthy carriers of *Entamoeba histolytica*. Stitt<sup>23</sup> takes the extreme view that *Giardia intestinalis* is "responsible for an intractable diarrhoea, an infection only minor in importance to amoebic dysentery."

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20 Porter, A. An Enumerative Study of the Cysts of *Giardia Intestinalis* in Human Dysenteric Feces, *Lancet* **1** 1166 (June 10) 1916.

21 Wenyon, C. M., and O'Connor, F. W. *Lambia Intestinalis*, *J. Royal Army Med. Corps* **28** 346 (March) 1917.

22 Hegner, R. W., and Payne, G. C. Surveys of the Intestinal Protozoa of Man, in Health and Disease, *Scientific Monthly* **12** 47 (Jan.) 1921.

23 Stitt, E. R. *Practical Bacteriology Blood Work and Parasitology*, Ed. 2, Philadelphia, P. Blakiston's Son & Co.

of the upper intestine. Their nutrition occurs by osmotic processes. In the duodenal contents they frequently present an extremely remarkable picture, the microscopic field literally swarming with these animalcules in a highly active state. When enmeshed in mucus they become motionless, only a few here and there showing sluggish movement. Following the injection of hypertonic solutions into the duodenum, flocculi from the duodenal crypts are extruded, and among the exfoliated duodenal cells small numbers of the parasites are frequently found. I found them in these duodenal flocculi in several instances in which none could be detected in the specimens of the fasting duodenal fluid. When carried from the duodenum into the lower intestine, they become encysted, unless they are hurried along by catharsis or diarrhea. It is easy to overlook the cysts in a routine examination of the feces with the low power lens. They are ellipsoidal and translucent and are slightly smaller than the active organism. Two or four nuclei are usually present. Sometimes they appear structureless. I found that the forms in the duodenal contents as well as those in the stools are well preserved in 10 per cent solution of formaldehyde. The important structures of the organism can be brought out by the addition of a weak iodine solution to the preparation, and are seen best by the oil immersion magnification.

#### TRANSMISSION

Authorities differ regarding the transmission of this infection. Since the active parasites die rapidly in the feces after expulsion, transmission between persons must take place by the ingestion of the cysts. Wenyon and O'Connor<sup>16</sup> and Stiles<sup>17</sup> have shown that flies can transfer the cysts. It has also been held, especially by Fantham and Porter,<sup>18</sup> who transmitted the infection from human patients to mice and kittens, that the contamination of food by the fecal discharges of these animals, especially by the "Dachshund rat" in the trenches, is an important factor in the spread of the infection in man. Recently, Simon<sup>19</sup> maintained that specific differences exist between the different forms of *Giardia*. *Giardia intestinalis* in man, *Giardia muris* in the rat and the mouse, and *Giardia microti* in the meadow mouse. He found that while rats could not be infected with cysts of *Giardia intestinalis* or *Giardia microti*, they could readily be infected with cysts of *Giardia muris*. He therefore concluded that the rat-mouse or meadow-mouse

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16 Wenyon, C. M., and O'Connor, F. W. The Carriage of Cysts of Intestinal Protozoa by House-Flies, *J. Roy. Army Med. Corps* **28** 522 (May) 1917.

17 Stiles, C. W. Flies as Carriers of *Lamblia* Spores, *Pub. Health Rep.* **28** 2530 (Nov. 28) 1913.

18 Fantham, H. B., and Porter, A. *Giardia Intestinalis*, *Brit. M. J.* **2** 139 (July 29) 1916.

19 Simon, C. E. Critique of Supposed Rodent Origin of Human Giardiasis, *Am. J. Hygiene* **2** 406 (July) 1922.

male fern, beta naphthol, bismuth salicylate and guaiacol carbonate Transduodenal lavage with solutions of methylene blue or magnesium sulphate is lauded by some The active flagellate is readily destroyed by these solutions Cures have occasionally been recorded, but it is doubtful whether they may be looked on as real, since the cases were not rigidly controlled In untreated cases the ova may be absent from the feces for long periods, and it is unsafe to consider a case as cured unless it is observed for a long time with frequent stool examinations Thus, Dobell and Low,<sup>30</sup> in examinations of the stools of a patient for 100 consecutive days, found them negative sixty-two days and positive thirty-eight days, with periods as long as ten successive days in which the examinations were negative The examination of the duodenal contents for the vegetative form gives more reliable data than the search for cysts in the stools When infection exists, it has been my experience that it is rare not to find the organisms either in the duodenal fluid or in the flocculi from the duodenal crypts following the injection of hypertonic solutions

It is difficult to eradicate the infection by drugs administered by mouth or introduced by transduodenal lavage, since the flagellates may lodge themselves in the digestive crypts outside the main lumen of the intestine, where they cannot be reached According to Smithies, they may even lodge in the gallbladder Such organisms can be attacked best by a drug excreted into these parts from the blood stream This was done experimentally in 1917, by Yakimoff and others,<sup>29</sup> who eradicated the infection in mice with intravenous injections of arsphenamin In corroborating this work, Kofoed and others,<sup>31</sup> showed in culture rats, that single injections of arsphenamin freed the animals of the infection only when given in four to eight times the human dose prorated to the body weight of the rat Smaller doses sometimes reduced the number of cysts, and a single dose, in an amount equivalent to the human dose, had little or no effect The effect of repeated injections of this last amount was not determined This was done in 1920 by Carr and Chandler,<sup>32</sup> who reported an apparent cure in a man judged by the disappearance of the cysts from the stools, following three injections of 0.6 gm at five-day intervals However, McGill<sup>12</sup> reported the persistence of the infection in a woman following four injections of from 0.3 to 0.6 gm of neo-arsphenamin at weekly intervals Goiffon and Roux<sup>28</sup> used arsphenamin with inconstant

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30 Dobell, C, and Low, G C A Note on the Treatment of *Lamblia* Infections, *Lancet*, Dec 23, 1916, p 1053

31 Kofoed, C A, et al On the Treatment of Giardiasis in Rats with Arsenobenzol, *J Med Res* **34** 293 (Jan) 1919

32 Carr, E I, and Chandler, W L Successful Treatment of Giardiasis in Man with Neoarsphenamin, *J A M A* **74** 1444 (May 22) 1920



Fantham and Porter found 187 cases of pure *Giardia intestinalis* infection among 1,305 soldiers suffering from diarrhea invalided to England from Gallipoli. It is stated by many that the virulence of the infection is greatly reduced in temperate climates. However, Fantham and Porter found that some of their most virulent cases came from Flanders. Woodcock and Penfold,<sup>24</sup> and Kennedy and Rosewarne<sup>25</sup> also report many cases of dysentery in soldiers from the trenches in which only *Giardia intestinalis* was found. Yakimoff,<sup>26</sup> on the firing line in the Caucasus, encountered numerous cases of dysentery in which *Giardia* alone seemed to be responsible. Cade and Hollande,<sup>27</sup> Goiffon and Roux,<sup>28</sup> and Deglos<sup>29</sup> reported cases of diarrhea due apparently to *Giardia*.

There was no history of diarrhea in the nine cases that I encountered. In fact, three of the patients had always been constipated. In none of them could the infection have been considered massive as judged by the number of cysts in the stools. It was difficult to determine the relation of this infection to the clinical symptoms that these patients presented, since other conditions were also present: duodenal ulcer, cholelithiasis, chronic cholecystitis, catarrhal jaundice and anacidity. One case was that of a neurotic girl, 24 years of age, who complained of vague intestinal rumblings and paresthesias. She also presented a sex complex. It was believed that possibly there was some relation between the *Giardia* infection and her abdominal complaints. However, following treatment, with complete eradication of the infection, she still complained bitterly of the same vague abdominal symptoms which could not be dissociated from her psychoneurosis.

While it appeared that *Giardia intestinalis* infection in these cases was merely incidental, the view must be entertained that when another pathologic process is present in the duodenum or gall tract it may be aggravated by the activity of these flagellates.

#### TREATMENT

The question of treatment is far from settled. The multiplicity of drugs suggested is evidence of their inefficiency as cures. Among the more common remedies suggested are calomel, turpentine, santonin,

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24 Woodcock, H. M., and Penfold, W. J. Protozoan Infections Occurring at the King George Hospital, Brit. M. J., March 18, 1916, p. 407.

25 Kennedy, A. M., and Rosewarne, D. D. Lamblia Intestinalis Infections from Gallipoli, Lancet 1 1163 (June 10) 1916.

26 Yakimoff, V. L., et al. Chemotherapy of Lambliosis, Russkiy Vrach 16 232 (March 11) 1917.

27 Cade, A., and Hollande, A. C. L'enterite a Giardia intestinalis, Arch. d. mal. de l'app. digestif 10 193 (July) 1919.

28 Goiffon, R., and Roux, J. C. Lamblia enteritis, Arch. d. mal. de l'app.

29 Deglos, F. Rôle of Lamblia in Intestinal Pathology, Lyon méd. 129 434 (May 25) 1920.

## SUMMARY

1 *Giardia intestinalis* infection is not rare. In the routine examination of the duodenal contents in 170 residents of New York City, nine cases of this infection were found.

2 While *Giardia intestinalis* is probably capable of producing a diarrhea of moderate severity, no symptoms attributable to this infection could be definitely established in the cases presented.

3 Three patients were treated with three arsphenamin injections in the usual doses at three to five-day intervals. This procedure was not successful in eradicating the infection in two cases. One case in which the injections were alternated with duodenal lavage with magnesium sulphate the patient remained free from the infection during fourteen examinations of the duodenal contents over a period of six months.

results Recently, Simon<sup>11</sup> reported the use of repeated injections of arsphenamin in several cases followed by the disappearance of cysts from the stools However, insufficient data are given regarding the frequency of the examinations, and the duration of observation to prove his patients cured

Of my series, three patients, whose cases are summarized below, submitted to treatment They were three women of approximately the same weight, and they received the usual doses of arsphenamin Only in the first case was a cure effected This case differed from the others in that a duodenal lavage with magnesium sulphate, for the purpose of recovering the parasite, was given between the intravenous injections Prior to the arsphenamin treatment repeated lavage with magnesium sulphate had failed to eliminate the organism It was believed at first that the disappearance of the parasite in this case was due to the action of the neoarsphenamin alone, therefore no duodenal lavage was given in the two subsequent cases However, in these two cases the infection reappeared It is possible that those organisms that are enmeshed in mucus, as in the duodenal flocculi, are protected against the action of the arsphenamin in the doses used Duodenal lavage with the hypertonic solution of magnesium sulphate can rid the host of such forms

#### AUTHOR'S CASES

CASE 1—Miss L G, aged 21, weight 102 pounds (46.26 kg) Diagnosis Neurosis

*Treatment*—May 9, 1922, 0.45 gm neo-arsphenamin

May 12, 1922, Duodenal lavage, 90 cc of 30 per cent of magnesium sulphate (No *Giardia* found in the duodenal contents)

May 13, 1922, 0.45 gm neo-arsphenamin

May 14, 1922, Duodenal lavage, 90 cc of 30 per cent of magnesium sulphate (No *Giardia* found in the duodenal contents)

May 16, 1922, 0.45 gm neo-arsphenamin

May 17, 1922, Duodenal lavage, 90 cc of 30 per cent of magnesium sulphate (No *Giardia* found in the duodenal contents)

*Result*—Fourteen examinations of the duodenal contents, up to six months since the last treatment, were negative for *Giardia*

CASE 2—Mrs F S, aged 31, weight 112 pounds (50.8 kg) Diagnosis Chronic cholecystitis

*Treatment*—June 6, 1922, 0.3 gm of arsphenamin

June 10, 1922, 0.3 gm of arsphenamin (Had arsphenamin reaction)

June 15, 1922, 0.2 gm of arsphenamin (Had arsphenamin reaction)

*Result*—Aug 26, 1922, duodenal examination *Giardia* present Stool negative for cysts

CASE 3—Mrs N D, aged 52, weight 118 pounds (81 kg) Diagnosis Anacidty

*Treatment*—July 1, 1922, 0.45 gm neo-arsphenamin

July 6, 1922, 0.45 gm neo-arsphenamin

July 11, 1922, 0.45 gm neo-arsphenamin

*Result*—July 30, 1922, duodenal examination *Giardia* present Stool, vegetative forms and cysts present

it to be of reflex origin due to sensitive nerves transmitting a morbid impression to the cord, which was thence reflected to the muscles. Gull,<sup>12</sup> in 1856, did not accept Stanley's views, and showed that the cord was actually altered. Hayem and Parmentier<sup>13</sup> drew attention to the frequency of gonorrheal arthritis with spinal phenomena. They believed that the nerve roots suffered an inflammatory reaction and that there must be a meningomyelitis. Charcot<sup>14</sup> expressed the opinion that such cases were only indirectly due to gonorrhea, that the spinal affection was arthritic in origin, and that the existence of arthritis was an essential preliminary. Nearly 55 per cent of the reported cases exhibiting no joint involvement have been decisive against this theory. Dufour<sup>15</sup> asserted that gonorrhea opens the door to secondary infections which bring about myelitis. The possibility of true gonorrheal metastasis to the spinal cord is conceded by Raymond and Cestan,<sup>16</sup> while Moltschanoff<sup>17</sup> seeks to demonstrate the effect of gonotoxin on the spinal ganglions of the nervous system. Whether the changes produced in the spinal cord are due to a gonotoxin, to the action of the gonococci themselves or to secondary invaders, has never been definitely established. Although neither bacteriologic examination of the spinal fluid nor sections of the cord have yielded gonococci in any of the examinations, we are inclined to believe that the changes must be due to the direct action of the gonococci themselves through metastasis to the cord. Were toxins alone to blame, it is reasonable to suppose that in the many severe gonorrheal infections seen, there would be more cases of spinal cord involvement, and again, nearly 45 per cent of instances of myelitis of supposed gonorrheal origin show also some complication of an evident gonorrheal metastatic nature, for example, arthritis. However, it may be, as O'Connor<sup>18</sup> states, that gonorrheal complications cannot be rigidly attributed to the gonococcus alone, but, as in every other infective disease, every complication has a complex etiology.

In a careful survey of the literature for reported cases of myelitis following gonorrheal urethritis, we were able to find twenty-nine instances which may be accepted either from a clinical standpoint or from the anatomic findings in conjunction with the history. Such records are those of Stanley,<sup>11</sup> two cases by Gull,<sup>12</sup> four cases by Hayem and Parmentier,<sup>13</sup> Charcot,<sup>14</sup> Dufour,<sup>15</sup> two reports by O'Connor,<sup>18</sup>

12 Gull *Med Chir Tr* **39** 195, 1856

13 Hayem and Parmentier *Rev de med* **8** 433, 1888

14 Charcot *Leçons sur les mal du syst nerv* **1** 3, 1880

15 Dufour *Thèse de Paris*, 1889

16 Raymond and Cestan *Rev neurol* **9** 171, 1901

17 Moltschanoff *Arch Russ de Path* **7**, 1899

18 O'Connor *Quart J M* **15** 69, 1921

## GONORRHEAL MYELITIS †

FRANK M PHIFER, MD, AND N K FORSTER, MD  
CHICAGO

The few cases reported in the literature of spinal cord involvement following a gonorrheal urethritis, and presumably due to a metastatic gonococcal infection or a gonotoxin, sufficiently support the possibility of such an occurrence, and it is the custom of textbook authors to devote a few lines to a general consideration of this subject. A careful search through the literature failed to uncover any reported cases or review of cases of this condition by investigators in this country, and the few scattered reports by others are contained in foreign journals. Because of the rarity of the condition and the fact that, so far as we have been able to determine, no review of reported cases has ever been made, we have compiled all available reports, and submit two such instances of our own.

Numerous records of gonorrheal meningitis are available, and while there has been considerable confusion and much discussion as to the diagnosis because of the similarity in characteristics of the gonococcus and the meningococcus, sufficiently controlled laboratory work has shown that the gonococcus may play the causative rôle in a meningitic infection. Cases reported establishing this fact both clinically and in the laboratory are those of Wooten,<sup>1</sup> Henderson and Ritchie,<sup>2</sup> Blind and Ricord,<sup>3</sup> Boivin,<sup>4</sup> Lindenfeld,<sup>5</sup> Malleterre,<sup>6</sup> Rombach,<sup>7</sup> Prochaska,<sup>8</sup> Chavrier and Fevrier,<sup>9</sup> and Gordon.<sup>10</sup> However, we have attempted to limit this paper to a consideration of cases in which there have been definite spinal cord changes without necessarily showing evidence of meningeal involvement.

Stanley,<sup>11</sup> in 1833, was the first to describe paraplegia occurring in the course of gonorrhea, calling it "urinary paraplegia," and believing

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† From the department of cystoscopy, skin and venereal diseases, Cook County Hospital, Chicago.

1 Wooten, J S. Acute Gonorrheal Meningitis, *J A M A* **32** 170, 1899.

2 Henderson and Ritchie. *Rev Neurol & Psychol* **7** 75, 1909.

3 Blind and Ricord. *Paris med* **21** 312, 1917.

4 Boivin. *Bull Soc med d hop de Paris* **43** 1024, 1919.

5 Lindenfeld. *Med Klin* **18** 176, 1922.

6 Malleterre. *New York M J* **103** 1024, 1916.

7 Rombach. *Nederlansch Tijdschr v Geneesk* **51** 1262, 1907.

8 Prochaska. *Deutsch Arch f klin Med* **83** 184, 1905.

9 Chavrier and Fevrier, quoted by O'Connor. *Arch de med*, Paris, 1888.

10 Gordon. *Diseases of the Nervous System*, 1917, pp 465 and 586.

11 Stanley. *Med Chir Tr* **18** 260, 1833. •

the admission of the patient, the reflexes were somewhat exaggerated, they soon became variable, and at the end of a week were abolished. Incontinence both of urine and feces was present from the time the patient was first seen, the urinary incontinence being of the paradoxical type. No evidence of pathologic changes in the spine could be made out.

*Laboratory Findings*—The findings were: red blood cell count, 4,960,000, white blood cell count, 11,400, differential white blood cell count: polymorphonuclears, 71 per cent, small lymphocytes, 12 per cent, large lymphocytes, 11 per cent, eosinophils, 1 per cent, transitionals, 5 per cent. Urine examination of a catheterized specimen showed a small amount of albumin with a large number of pus cells and a few red blood cells. Smears from the urethra discharge disclosed a large number of gram-negative intracellular and extracellular diplococci, in typical gonococcal arrangement, which were recovered as such on culturing. Smears from the expressed prostatic and seminal secretions likewise showed similar organisms with a large number of pus cells. Spinal fluid examination revealed a clear fluid under no increased pressure, no increase in the cell count and no globulin with the Ross-Jones, Nonne and Pandy tests. Direct smears of the spinal fluid sediment revealed no organisms. Cultures in broth and on blood agar and Löffler's serum, as well as on dibasic sodium phosphate ascitic agar, remained sterile up to the third day. In sugar broth, smears revealed a gram-positive coccus, while agar cultures from this broth remained sterile, probably a contamination. Roentgen-ray examination of the dorsolumbar spine failed to show any pathologic condition, while a tendency toward an osteo-arthritis was noted in the sacro-iliac articulations. The blood Wassermann test was negative, as was that of the spinal fluid. The Lange reading on the spinal fluid was 0001110000. Blood chemistry determination gave the following figures: total nitrogen, 2750, nonprotein nitrogen, 2800, urea nitrogen, 38.29, urea, 81.94, uric acid, 340 and creatinin, 1.67. A blood culture remained sterile after forty-eight hours.

*Treatment and Course*—Little elevation of temperature occurred, and the condition of the patient generally was good. Urination by overflow was established, and urinary antiseptics given. His condition remained stationary until fourteen days after admission, when he developed a right epididymitis. Intravenous injection of a polyvalent gonococcus vaccine was given and followed by some relief and diminution of the swelling of the affected epididymis. On the fifteenth day there was evidence of a beginning decubitus ulcer despite the careful measures taken to prevent this. The patient was placed on his abdomen on a Bradford frame, and all friction points carefully padded. However, the sacral ulcer continued to form, and finally exposed the sacrum for an area of about 12 cm in diameter. There was marked edema of the scrotum and penis, his condition became progressively worse and was accompanied by a universal toxic erythema. Death occurred on April 29, 1922, thirty-nine days after admission to the hospital and forty-three after the onset of the symptoms.

Measures undertaken to secure a necropsy were unavailing, except for an examination of the brain. This proved negative both grossly and histologically, except for a moderate amount of edema.

*CASE 2—History*—I. M., aged 26, single, an American, a chauffeur, entered Cook County Hospital on Jan. 28, 1920, complaining of inability to urinate, difficulty in walking, and numbness and tingling of the lower extremities. He states that until the day preceding his entrance into the hospital he had been perfectly well, except for a chronic discharge from the penis, which had its onset in March, 1919, and, following a temporary respite, had recurred in October 1919, to persist up to the present time. Two days previous to his admission he first experienced some difficulty in urinating, chiefly marked by straining and some dribbling. The following day he was unable to void, was nauseated, vomited, had chills and some fever, and first noticed a tingling and numbness in his lower extremities, which, however, did not prevent his getting

Eulenberg,<sup>19</sup> four instances by Delamare,<sup>20</sup> Peter,<sup>21</sup> Tixier,<sup>22</sup> two cases by Spillmann and Haushalter,<sup>23</sup> von Leyden,<sup>24</sup> Speranski,<sup>25</sup> Pissavy and Stévenon,<sup>26</sup> Olmer,<sup>27</sup> Rogalsky,<sup>28</sup> Luys,<sup>29</sup> Gowers,<sup>30</sup> and Raynaud's<sup>31</sup> report of one case of Moreau's and one of Gemy's To these we wish to add the reports of two cases of our own

#### REPORT OF CASES

**CASE 1—History**—Mr J S B, aged 23, single, Swedish, a salesman, entered Cook County Hospital on March 20, 1922, complaining of inability to walk or move his legs, inability to urinate and discharge from the penis He said that about two weeks previously he had first noticed the urethral discharge coming on seven days after exposure in intercourse He had endeavored to treat himself with various hand injections, and until four days ago had experienced no unusual symptoms At this time he first noticed a feeling of weakness in both lower limbs However, he remained up and about and paid little attention to the condition The following morning the weakness was more marked, and during the course of the day he experienced several chills lasting ten or fifteen minutes, followed by sweating and fever The weakness became progressively worse so that by evening he was confined to his bed The following day he was able to be up on his feet for short periods, but began experiencing some difficulty in voiding urine, and by evening this partial retention became complete so that it was necessary to catheterize him, a condition which had persisted until the time of his entrance into the hospital The following day, which preceded his coming to the hospital, he was unable to stand or walk, or even to move his lower limbs—a paralysis which has remained unchanged

The past history was negative, except for the usual childhood diseases and the removal of the tonsils The venereal history disclosed three previous gonorrheal infections The family history was essentially negative

**Physical Examination**—This disclosed a well nourished male adult who, beyond his inability to walk, did not appear acutely ill Regional examination proved to be negative or normal in all essentials, with the exception of the genitals and the extremities A profuse purulent discharge exuded from the urethra, the bladder extended about three fingerbreadths above the symphysis by percussion, the prostate was only slightly enlarged and not excessively tender, although giving a false impression of enlargement because of the distended bladder The testicles were both present in the scrotum and with their epididymides presented no abnormal findings The extremities exhibited a flaccid paralysis, although this was not complete, the patient being able to move his toes slightly, and there was some response to the effort to bend the right knee Complete anesthesia both anteriorly and posteriorly up to the level of the anterior spines of the ilium was present On

19 Eulenberg *Deutsch med Wchnschr* **36** 686, 1900

20 Delamare *Gaz d hop de Paris* **76** 549, 1901

21 Peter *Gaz hebdomadaire de med* **3** 764, 1866

22 Tixier *These de Paris*, 1866

23 Spillmann and Haushalter *Rev de med* **11** 651, 1891

24 Von Leyden *Ztschr f klin Med* **21** 607, 1892

25 Speranski *Med Oboz Moskow* **39** 770, 1893

26 Pissavy and Stevenon *Bull Soc med d hôp de Paris* **24** 919, 1907

27 Olmer *Rev neurol* **18** 115, 1910

28 Rogalsky *Tunisie med*, Oct, 1912, p 313

29 Luys *Gonorrhea and Its Complications*, London, 1913, p 226

30 Gowers *Med Press and Circ*, London **89** 249, 1910

31 Raynaud *Rev de med* **12** 183, 1892

health, with the exception of an acute and a chronic gonorrhea, the evidence from a clinical standpoint in favor of this is extremely strong, and certainly these two cases approximate in all their aspects those reported in the literature as gonorrheal myelitis

A review of the reported case histories found in the literature shows the occurrence of this condition in twenty-six males and three females. The age incidence was between 15 and 40 years, with the greatest number occurring between the ages of 18 and 30. The gonorrheal urethritis was determined as acute in one case, chronic in twenty-three instances and not given in five. The number of infections ranged from one to "numerous," the largest number given being three. The duration of the infection at the time the patient presented the symptoms of myelitis ranged from "recent" to twelve years, the majority occurring between two months and a year after infection. Of the twenty-nine cases, fourteen patients, or nearly 45 per cent, suffered from a gonorrheal complication, of which twelve were arthritic in nature chiefly involving the knees, there was one case of endocarditis, and one of nitis which were considered to be of gonorrheal origin. The onset where mentioned was sudden in all of the cases. Twenty-two of the cases began with pain in the back and along the thighs, to be shortly followed by the nervous manifestations, in two, the mode of onset was without premonitory symptoms. The sphincters were not involved in seven cases, while sensation was undisturbed in two. The presence of a decubitus ulcer was mentioned in four instances. All of the patients showed motor loss in greater or less degree, and the reflexes were correspondingly involved. Of the twenty-nine patients, eight, or about 24 per cent, died, of which number six went to necropsy, with the resulting anatomic diagnosis of myelitis. The length of time elapsing between the onset of the paralysis and death varied from sixteen hours to four months. In two instances only were bulbar phenomena mentioned. Complete recovery occurred in ten cases, or 34 per cent, recovery with one recurrence took place in one case, and recovery with four recurrences in one case. One patient was still in the hospital at the time of the report, and three left the hospital before recovery, while in four instances the outcome was not mentioned.

Delamare has divided these cases into acute, subacute and chronic manifestations, while Pissavy and Stévenon think that a good dividing line between slight and severe forms is struck by the presence or absence of sphincter troubles. All of the cases exhibiting acute onsets and symptoms died, and accepting Delamare's division, we have found eight of the acute type, three subacute and eighteen of the chronic form of myelitis.

The pathologic changes so far as the spinal cord is concerned, depend on the stage of degeneration and the severity of the inflam-



about On the morning of his admission, however, he said that his limbs were very weak, and in walking he was forced to drag his legs and to spread them far apart, then with considerable effort he was able to move about With the exception of diphtheria in 1914, his past illnesses were limited to the usual childhood diseases The venereal history dated from March, 1919, when the initial gonorrhea occurred He denied ever having had a chancre The family history was unimportant

*Physical Examination*—This disclosed a white adult male, well nourished and developed, and apparently not acutely ill The bladder on percussion was found four fingerbreadths above the symphysis The urethra discharged a heavy yellow pus, while the testicles and epididymides were normal The prostate was slightly enlarged and tender, although not markedly so The lower extremities were cyanotic and cold, and exhibited a marked loss of motor and sensory power However, there was not a complete paralysis, as the patient was able to bend both knees slightly, as well as flex and extend the toes, and motion from the hip joint was not entirely gone The reflexes were exaggerated, with slight ankle clonus and absent Babinski sign There was a noticeable loss of sensation, especially along the anterior surfaces, extending as high as the umbilicus, where a hyperesthetic zone was found Cystoscopic examination was made, a 24 F catheterizing cystoscope passing without obstruction The bladder was tolerant to fluid and instrumentation, and 28 ounces (800 cc) of retained urine was secured Marked atony of the bladder existed, the entire floor sagging, while a moderate silky trabeculation was present The ureteric orifices were seen to be greatly dilated, and no rhythmic contractions or efflux was present The entire cystoscopic picture was that seen in typical cases of cord lesion bladders Both kidneys were catheterized and specimens secured for cultural study

*Laboratory Findings*—Red blood cell count was 5,100,000, white blood cell count, 9,800 Urine examination revealed albumin in small amounts with many pus cells and a few red blood cells Catheterized kidney specimens revealed normal findings for both sides, chemically, culturally and microscopically Smears from the urethral discharge showed many pus cells and a large number of gram-negative intracellular and extracellular diplococci The blood Wassermann test was negative, as was that on the spinal fluid Examination of the spinal fluid revealed a clear fluid under slightly increased pressure, with negative globulin reactions and no increase in the cell count The Lange curve read 0011110000 Direct smears from the sediment revealed no organisms, and cultures on blood agar and Löffler's serum, as well as in broth, remained sterile after forty-eight hours A radiogram of the dorsolumbar region failed to reveal any spinal pathologic condition

*Course*—Incontinence of urine and feces persisted until twelve days after admission, when he slowly began to recover the power of voluntary urination and defecation This was followed by a more rapid improvement in the motor function of the lower extremities, so that twenty-five days after admission and twenty-seven days after the onset of the symptoms, he was discharged from the hospital While at this time he was still somewhat weak he was able to move about with only slight dragging of the legs and straddling He was able to control the act of urination without straining or dribbling, and to all obvious symptoms was well on the way to entire recovery This patient was seen again three years later, and at this time exhibited no symptoms of his former difficulty and was apparently in perfect health

#### COMMENT

While it has been impossible to prove definitely the gonococcus as the etiologic factor in these cases from the standpoint of laboratory findings, it must be conceded that in two persons who were in perfect

the onset is slow, all extremities are involved, particularly the extensors, while the bladder and rectum are rarely affected, and trophic changes are not seen. In Landry's paralysis, there is a steady advance of the paraplegia from the lower extremities upward, with undisturbed sensation, retention of bladder and rectal control and reflexes. In hysteria, reflexes are not disturbed, trophic changes are not present, and hysterical stigmas are obtainable, while the sensory disturbance has a characteristic outline. With the exclusion of all other possible causative agents, the basis for the assumption that the gonococcus, in a patient suffering from a gonorrheal infection, is the causative factor producing the myelitis is perfectly logical.

The prognosis is, of course, dependent on the changes present in the individual case, but in general it is to be considered grave as to life and certainly as to complete recovery.

The treatment in these cases is chiefly symptomatic, while the attempt is made to prevent the development of complications. The wisdom of attempting to eradicate the focus in the urethra by active measures directed to the posterior urethra is debatable, and in our opinion efforts directed toward the building up of the general body resistance will prove more effective. The danger of an ascending urinary infection is great, and it has been our experience in dealing with myelitis from any cause that the establishment of urination by overflow is not desirable. By means of a small suprapubic puncture with the insertion of a catheter for drainage through a cannula, as in dealing with an empyema by the closed method, it is possible to secure adequate drainage and to carry out systematic lavage of the bladder. The use of a Bradford frame, or a water or air bed, with careful padding of all pressure points is essential in the avoidance of dystrophic bedsores. The nutrition of the muscles should be maintained by intelligent massage or electrotherapeutic measures from the beginning, and the position of the limbs should be frequently changed. The general physical condition should be watched carefully, and beyond the usual symptomatic measures, the treatment resolves itself to the prevention of complications.

matory process There is usually flattening of the cord at the seat of the lesion, and at this point it is much softer than the remainder On section, the distinction between the gray and white matter is lost or indistinct The microscope will show swelling and distortion of the nerve fibers, beading of the axis cylinders, abundant myelin droplets and sometimes corpora amylacea Swelling of the ganglion cells with granular and vacuolated protoplasm, distended veins, leukocytic infiltration and degenerated nerve fibers are seen Following the acute stage, the so-called red or inflammatory softening is succeeded by fatty degeneration, and a change in color to yellow and finally white as sclerosis sets in

The symptoms are those common to myelitis from any cause The onset is usually sudden, and the symptoms not long in manifesting themselves There may be pain in the legs or back, or a girdle sensation, together with chills and sometimes convulsions Motor functions are rapidly lost, and following hyperesthesia sensation is disturbed Early the reflexes are exaggerated, later becoming variable and finally abolished The rectal and bladder sphincters are paralyzed, and there is usually wasting of the muscles and trophic disturbances, while the temperature of the affected parts is lowered, and decubitus ulcers make their appearance The myelitis may be of an ascending type, with cervical paraplegia, bulbar symptoms and death In the acute cases the symptoms become aggravated, the pulse rapid, the tongue dry and delirium sets in to be followed by coma and death Patients with subacute and chronic cases usually recover, although the paraplegia may persist for some time, and occasionally there are recurrences, while trophic changes are not marked, and sphincter disturbances may be absent

The diagnosis in these cases must be made chiefly by exclusion, and for this purpose a comprehensive history, a thorough physical examination with special attention to the neurologic findings and reliable laboratory determinations must be secured The rapid and progressive motor paralysis, the relaxation of the sphincters, corresponding sensory disturbances or anesthesia surmounted by a band of hyperesthesia, the muscular atrophy, exaggerated reflexes below the site of the lesion and the loss of faradic response in the muscles together with trophic changes and decubitus ulcers determine the question as to the presence of a myelitis The origin must be determined from the history, the evidence of traumatism, acute infectious diseases, syphilis, septicemia and spinal cord tumors Among the conditions to be differentiated are chiefly poliomyelitis, meningitis, multiple neuritis, Landry's paralysis and hysteria In poliomyelitis, the motor loss is usually of the monoplegic type, and sensory changes are generally absent In meningitis there is retention of motor power and reflexes In multiple neuritis

invade or infiltrate the surrounding tissues but often cause marked displacement of the viscera. In Hodgkin's disease the lungs may be infiltrated giving the impression of a tuberculous process. In roentgenograms they are represented by shadows which are usually oval or elongated and appear either singly or massed together.

According to Kahn,<sup>4</sup> "lymphosarcoma usually manifests itself as a large single shadow and may occupy the greater part of the chest

Hodgkin's disease roentgenologically resembles somewhat lymphosarcoma, indeed the mediastinal shadows of these two diseases cannot be absolutely differentiated."

Childs<sup>5</sup> asserts that "lymphosarcoma starts in the mediastinum and is apt to increase rapidly in size and involve the lung or pleura or both.

Hodgkin's disease is generally shown by a paratracheal, dense shadow projecting beyond the mediastinum with a border either irregular in outline or circumscribed and clearly defined, which extends over a considerable part of the median shadow. These masses may attain to a large size, projecting beyond the mid-clavicular nipple line, and extend the entire length of the median shadow. Occasionally only a unilateral mass projects at the level of the hilus, circumscribed by a border similar to that above described."

In the work of Lemon and Doyle,<sup>6</sup> "Hodgkin's disease is suspected when the roentgenogram reveals a bilateral feathery shadow passing outward from each hilus." And as to the value of radiographic evidence "A pathologic diagnosis hardly should be expected from the roentgenographic findings but in eight cases (out of twenty-six) a positive opinion was reached."

#### RADIOGRAPHIC APPEARANCES IN HODGKIN'S DISEASE AS INTERPRETED FROM THE PATHOLOGY

To best interpret the radiographic appearances of Hodgkin's disease it is necessary to have a clear picture of the gross pathology in mind as the plate is being examined.

The enlarging glands form more or less lobulated tumor masses, the lobules being rather smooth and discrete, varying from the size of a pea to that of a hen's egg or larger. Since the glands are fairly

<sup>4</sup> Kahn, M. X-Ray Studies of Mediastinal Shadows with Special Reference to Dermoid Cyst, *J Radiol* **3** 45, 1922.

<sup>5</sup> Childs, S. B. New Growths Within the Chest. *Am J Roentgenol* **10** 3-175, 1923.

<sup>6</sup> Lemon, W. S., and Doyle, I. B. Clinical Observations on Hodgkin's Disease with Special Reference to Mediastinal Involvement. *Am J M Sc* **162** 525, 1921.

<sup>7</sup> Longcope, W. T. and McAlpin, K. R. Hodgkin's Disease, *Oxford System* **4** 1, 1921. MacCallum, W. G. *Textbook of Pathology* Philadelphia W. B. Saunders Company 1920 p 853.

# MALIGNANT LYMPHOMA (HODGKIN'S DISEASE)

## A RADIOGRAPHIC STUDY

LESTER R WHITAKER, MD

CAMBRIDGE, MASS

This investigation of Hodgkin's disease is based on the study of forty cases examined radiographically at the Massachusetts General Hospital and seven cases of which necropsies were made

Hodgkin's disease is often confused in diagnosis with other conditions, especially tuberculosis, and patients are thus denied the benefits of roentgen-ray therapy One patient in our series was sent to Arizona for tuberculosis, only to find out later that the long trip was to no purpose

The chest is the most fruitful field for radiographic examination in this disease because the low density of the lungs allows masses of lymphomatous tissue to show up well, and because the chest is often involved—seven out of twenty-two cases which came to necropsy

The radiographic appearance is characteristic enough to be of great value in the differentiation from other forms of malignancy and tuberculosis

## REVIEW OF THE LITERATURE

References to the radiographic diagnosis of Hodgkin's disease are to be found chiefly in articles dealing with the radiographic diagnosis of mediastinal tumors and other intrathoracic conditions The only article dealing primarily with the radiographic findings in Hodgkin's disease which I was able to find is one by Wessler and Greene,<sup>1</sup> to be discussed later Since I shall discuss the relation between Hodgkin's disease and lymphosarcoma, quotations will be made from the literature on these two subjects

Thomas<sup>2</sup> says that "lymphosarcoma is the most frequent mediastinal growth There may be observed distinct indications of irregular involvement of the adjacent tissues In Hodgkin's disease the involved glands are apt to be quite large and discrete"

Walton<sup>3</sup> sees in lymphosarcoma "irregular growths with sharply defined outlines often somewhat nodular in shape and extending far beyond the limits of the mediastinum These tumors do not tend to

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1 Wessler, H, and Greene, C M Intra-thoracic Hodgkin's Disease Its Roentgen Diagnosis, J A M A **74** 445 (Feb 14) 1920

2 Thomas, George F The Roentgen Diagnosis of Lesions in the Region of the Mediastinum, Am J Roentgenol **1** 133, 1914

3 Walton, H J Roentgenological Examination of the Mediastinum Am J Roentgenol **5** 181, 1918

Seven of our forty patients had pleural effusions, five in the left, and one in both pleural cavities (Figs 10 and 11). Lemon and Doyle<sup>4</sup> found fluid in four out of twenty-six cases.

#### TYPES OF INTRATHORACIC INVOLVEMENT IN HODGKIN'S DISEASE ACCORDING TO RADIOGRAPHIC FINDINGS

Wessler and Greene,<sup>1</sup> from a study of twenty-five cases radiographically, have divided intrathoracic involvement in Hodgkin's disease into four groups.

*Group 1—Mediastinal Tumor.* These are masses extending out from the mediastinum into the lungs—eight of the twenty-five cases. Twenty-two of our forty cases showed this condition (Figs 3, 4, 12 and 13).

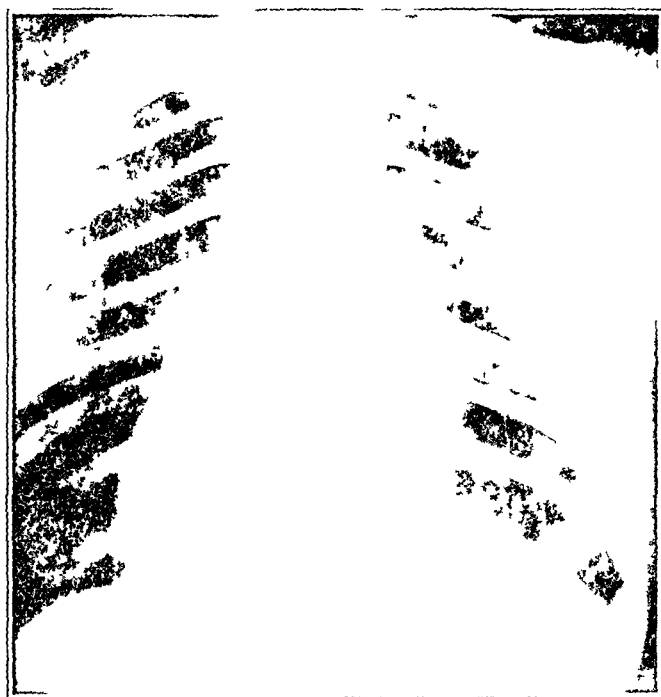


Fig 2—Hodgkin's disease. Typical nodular shadows at right hilum, slight upper mediastinal involvement. A man, aged 26, for four months had severe pain in the hips, legs and back. He had a wheezy cough at night, but there was no sputum. His appetite was poor, he lost 15 pounds (68 kg) in six months. There had been no exposure to tuberculosis and there was none in his family. Physical examination revealed small discrete nodes in the neck, dullness over the upper four dorsal vertebrae, supracardiac dullness, 9 cm. Blood examination revealed a white blood count of from 19,000 to 33,000 polymorphonuclears, from 80 to 92 per cent, lymphocytes, from 2 to 11 per cent, large mononuclears, from 6 to 10 per cent, eosinophils, from 1 to 2 per cent. The red blood count was 3,900,000, and hemoglobin from 50 to 80 per cent. In the evening, the temperature rose to from 102 to 103 F, with morning remissions lasting twenty days, ten days after roentgen-ray treatment. The biopsy report was malignant lymphoma.

*Group 2—Infiltrative Type, four cases.* "Borders of the infiltrating mass are indistinct and irregular. It may be a diffuse transformation of

dense and homogeneous the radiographic appearance is somewhat like a silhouette of a lobulated mass extending into the lung field

The glands vary considerably in density because fibrosis in them is progressive. The result is that in early cases the radiographic shadows are less dense than in older cases, and sometimes the outlines of several lobules can be distinctly seen (Figs 2 and 14). In older cases, the lobulation may be lost and the appearance of a large tumor mass may be seen in the mediastinum (Figs 3 and 4). Matting of the nodes together by fibrosis occurs after secondary infection or roentgen-ray treatment.<sup>8</sup> On account of this fibrosis, the large tumor masses of

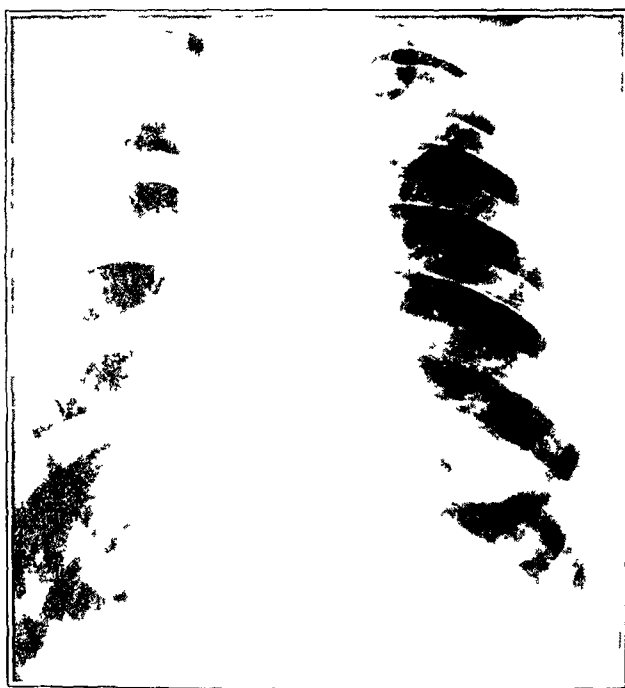


Fig 1—Normal chest, some evidence of peribronchial thickening, but within normal limits

Hodgkin's disease seldom have the regular outlines of an aneurysm or mediastinal carcinoma

Occasionally in late or acute cases, instead of expanding evenly, the lymphomatous masses infiltrate the lung tissue,<sup>9</sup> extending out from the hilus and giving somewhat the appearance of the peribronchial thickening and diffuse clouding of the lung fields seen in bronchopneumonia (Figs 6, 7, 8 and 9)

Two of the seven cases that came to necropsy had lymphomatous infiltration of the lungs (Figs 8 and 9)

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<sup>8</sup> Footnote 6 Longcope Footnote 7

<sup>9</sup> Footnotes 1 and 3



Fig. 3—Late case of Hodgkin's disease with upper mediastinal involvement. Two years ago, a man, aged 35, noticed a nodular ridge above the right clavicle which grew slowly. There were no symptoms until nine months before when slight dyspnea and dysphagia began gradually increasing. Physical examination revealed large nodes in the neck and axillae, hard, painless, discrete and freely movable. The chest findings were dulness, bronchial breathing and rales over the upper halves of both chests. This was a typical case of Hodgkin's disease, and roentgen-ray treatment gave marked relief.



Fig. 4—Same case as in Figure 3 after six months of roentgen-ray treatment.



intra-pulmonary lymphatic tissue into granuloma" (Wessler and Greene) Eleven of our cases showed this condition (Figs 6, 7, 8 and 9)

This may represent the condition which some classify as lymphosarcoma<sup>10</sup>

*Group 3*—Isolated Nodules or Metastases in the Lung Four cases "Circular or oval shadows of moderate density, usually one to several centimeters in diameter Probably these shadows are due to the development of lymphomatous foci in pre-existing lymphatic tissue (Wessler and Greene)

None of our series showed this condition clearly on the radiograph although one of the seven cases that came to necropsy did show masses of lymphomatous tissue 1 to 3 cm in diameter in the upper lobes (Fig 8)

One possible source of error in interpreting oval or circular shadows a few centimeters in diameter is that they may represent fibrotic areas of some old pathologic process For instance, two of our seven at necropsy showed foci of obsolete tuberculosis in the lungs

*Group 4*—Discrete Nodes at the Roots of the Lungs Seventeen cases "This is the most common type The shadows often extend for a considerable distance from the roots of the lungs and retain a definite outline The shadows are rather faint, differing in this respect from other forms of malignancy and tuberculosis" (Wessler and Greene)

Thirty-three of our forty cases showed this condition radiographically, being by far the most common type of involvement in our series as well as in theirs (Figs 2, 14 and 15)

The faintness of the shadows mentioned by Wessler and Greene may be due to young lesions before much fibrosis has taken place in the nodes It would seem that homogeneity of the shadows is a more important factor in their differentiation from tuberculosis In that disease, the shadows are of irregular density showing some very dense spots due to calcification

In fourteen of their twenty-five cases they noted an involvement of the right paratracheal nodes, they considered this a factor of importance in differentiating Hodgkin's disease from tuberculosis and other forms of malignancy, except in the tuberculosis of children in which these glands are often affected

Seventeen of our forty cases showed this condition, or at least showed a widening of the upper mediastinal shadows (Figs 2, 12 and 13)

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10 Footnotes 2 and 5



Fig 7 Same case as in Figure 6 The lymphoma is reduced in size and density as the result of five months of roentgen-ray treatment



Fig 8—Hodgkin's disease with nodules of lymphomatous tissue in the lungs at necropsy There was a lymphoma of the bronchial glands, with masses of lymphomatous tissue from 1 to 3 cm in diameter in the upper lobes The roentgenogram indicates a diffuse peribronchial process involving chiefly the hilum and upper lobes The small, indistinct shadows in the lung fields may indicate infiltrating masses of lymphoma or they may indicate fibrotic areas of an old inflammatory process



Fig 5—Carcinoma of the mediastinum A man, aged 53, had dyspnea and dysphagia, with slight dulness at the apexes of the lungs and at the left base. Fluoroscopic examination revealed a nonpulsating mass behind the heart, trachea and esophagus, and slight erosion of the bodies of the vertebrae. The roentgenogram showed a large, clearly outlined mass so dense that its borders were seen through the heart. The diagnosis was mediastinal carcinoma.



Fig 6 Hodgkin's disease with infiltration of the lung. There were enlarged nodes in the neck three months before this roentgenogram was taken, but the lungs were negative at that time.

## NECROPSY FINDINGS

Of our series of seven cases of malignant lymphoma with intra-thoracic involvement which came to necropsy, six showed mediastinal involvement, three hilus nodules two lung infiltration and one isolated nodules of lymphomatous tissue in the lungs

I believe that the best method of approach to a problem of this kind is an interpretation of the radiographic appearances from the pathology of the disease under consideration. In any given case the pathology varies with the course of the disease and there is reason to think that the radiographic appearances would vary also. A case which at first would come under the mediastinal or hilus type might later become infiltrating.

## DIFFERENTIAL DIAGNOSIS

*Lymphosarcoma*—The knowledge of the pathology of this tumor is so indefinite that lymphosarcoma cannot be said to be essentially different from Hodgkin's disease. MacCallum<sup>11</sup> believes that the two conditions are distinct while Bunting<sup>12</sup> holds the opposite opinion. Mueller<sup>13</sup> has presented evidence that lymphosarcoma is a rapidly progressive form of Hodgkin's disease. The term malignant lymphoma, which many pathologists apply to Hodgkin's disease, would seem to include lymphosarcoma. We agree with Kahn<sup>4</sup> that the two conditions cannot be differentiated radiographically. Figures 6, 7 and 9 might very well represent lymphosarcoma.

*Metastatic Sarcoma*—Metastases in sarcoma are usually blood borne. They commonly spring up in the lung parenchyma giving definite radiographic shadows in the lung fields. Figure 16 shows dense well defined shadows at the bases, partly obscuring the heart shadow. They resemble somewhat those of Hodgkin's disease. In the latter condition however tumors spring up in preexisting lymph nodes, which places the shadows usually in the hilus or upper mediastinal regions.

*Carcinoma*—The growths in carcinoma are in general denser and even more discrete than those of lymphoma, with the result that the radiographic shadows are more definite and have sharper outlines (Figs. 5 and 17). Metastatic carcinoma often shows isolated nodules in the lung substance which cast pronounced radiographic shadows.

11 MacCallum, W. G. On the Pathological Anatomy of Lymphosarcoma and Its Status with Relation to Hodgkin's Disease, Bull. Johns Hopkins Hosp. **18** 337, 1907.

12 Bunting, C. H. Lymphosarcoma, Nelson's Loose Leaf System of Medicine **3** 366.

13 Mueller, T. Relation of Hodgkin's Disease to Sarcoma, J. Med. Res. **42** 325, 1921.

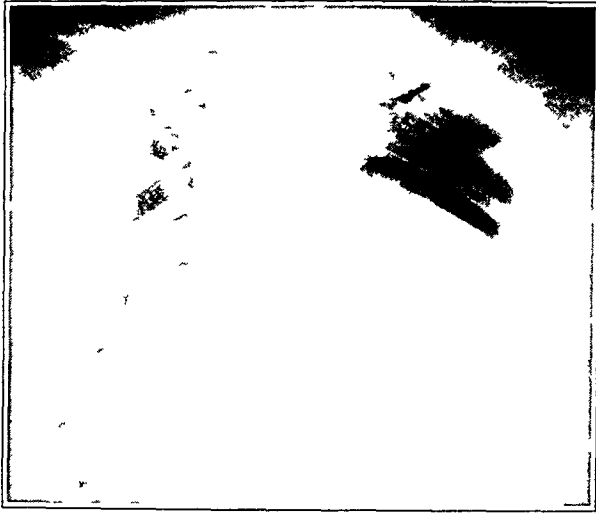


Fig 9—Hodgkin's disease, rapidly fatal Necropsy revealed lymphoma of the mediastinal and bronchial lymph nodes infiltrating the lungs and involving the pleura This might have been a case of lymphosarcoma



Fig 10—Hodgkin's disease with fluid A man, aged 39, had a cold and a cough nine months before this roentgenogram was taken The loss of 10 pounds (4.5 kg) of body weight was followed by wheezing and dyspnea on exertion Physical examination revealed general glandular enlargement From the right pleural cavity, 1,500 cc of straw-colored fluid, with a specific gravity of 1.020, and clotting quickly, was removed The enlarged, definitely outlined shadow suggests a lymphomatous growth



Fig 11—Same case as in Figure 10, three months later



Fig 12—Hodgkin's disease, with upper mediastinal involvement. A man, aged 28, one year ago noticed a swelling in the neck, but he had no other symptoms. Physical examination revealed shotty, discrete, bean-sized lymph nodes in the neck and axillae, with supracardiac dulness 11 cm in the first interspace, and D'Espine's sign to the tenth dorsal vertebra. The temperature, from 99 to 100 F for the first six days in the hospital, was reduced by roentgen-ray treatment. According to the blood count, there were from 14,000 to 19,000 white blood corpuscles, 76 per cent polymorphonuclears, 10 per cent lymphocytes, 14 per cent large mononuclears. The biopsy report was malignant lymphoma.

Wessler and Greene have seen radiographic evidence of isolated nodules in the lungs in four of their twenty-five cases of Hodgkin's disease. None of our cases gave this evidence on the plates, although one of the seven cases on which necropsy was performed had lymphomatous nodules in the lungs (Plate 8). MacCullum<sup>14</sup> found numerous large discrete nodules scattered in the lung tissue in one case at necropsy.

We believe that isolated shadows, in the lung fields, circular or oval in shape and rather dense, are good evidence against Hodgkin's disease and in favor of metastatic carcinoma or sarcoma.

*Enlarged Hiluses and Chronic Inflammatory Processes*—The size of the shadows at the roots of the lungs varies so greatly that it is difficult to determine their normal limits. Every inflammation or irritation, acute or chronic, supposedly contributes to a thickening of the nodes about the lung roots.

Occasionally a hilus shadow has a distinct outline or a suggestion of lobulation which resembles Hodgkin's disease.

In Figure 18, both hilus shadows are thickened. That on the right has a distinct outline. The fact that it is not lobulated and tapers to a point toward the base of the lung is evidence against Hodgkin's disease. The patient had tertiary syphilis with dyspnea and aphonia.

*Tuberculosis*—By far the most important condition to differentiate from Hodgkin's disease is tuberculosis. Tuberculosis might be considered a glandular disease, since the lymph nodes are almost constantly involved secondarily to focal infection. Many believe Hodgkin's disease has a similar origin.<sup>12</sup> These diseases are almost similar, both from a clinical and a pathologic point of view. This results in many erroneous diagnoses and much disadvantage to patients.

The prime reason for early differentiation of Hodgkin's disease from pulmonary or glandular tuberculosis is that roentgen-ray treatment, even though it does not cure, prolongs the lives and greatly enhances the comfort of patients with Hodgkin's disease.<sup>15</sup>

*Comparative Pathology of Tuberculosis and Hodgkin's Disease*—There may be generalized or localized glandular enlargement in both diseases. The glands about the roots of the lungs are commonly affected in both, often in tuberculosis, and occasionally in Hodgkin's disease, they are the only glands affected,<sup>6</sup> so that radiographic differentiation becomes important.

The difference in the intrathoracic pathology of the two conditions is that Hodgkin's disease, so far as our investigation has been able to

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14 MacCullum      Footnote 7

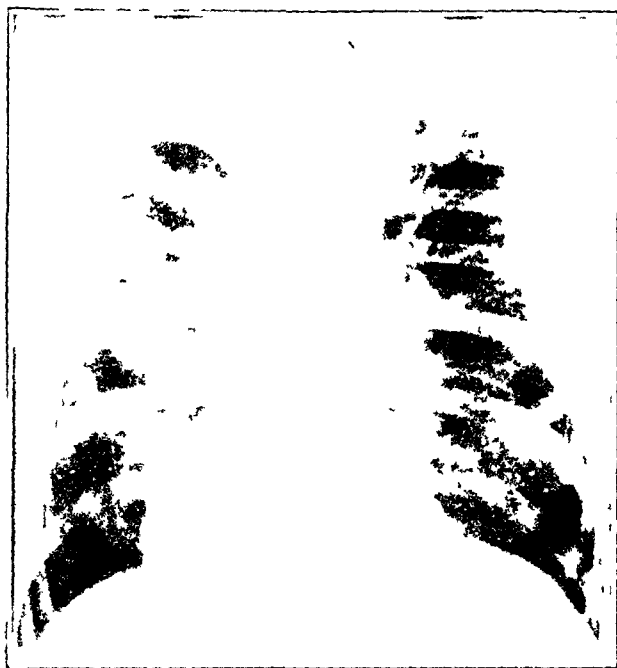


Fig. 15—Same case as in Figure 14. The roentgenogram shows the reduction in density after five months' roentgen-ray treatment.

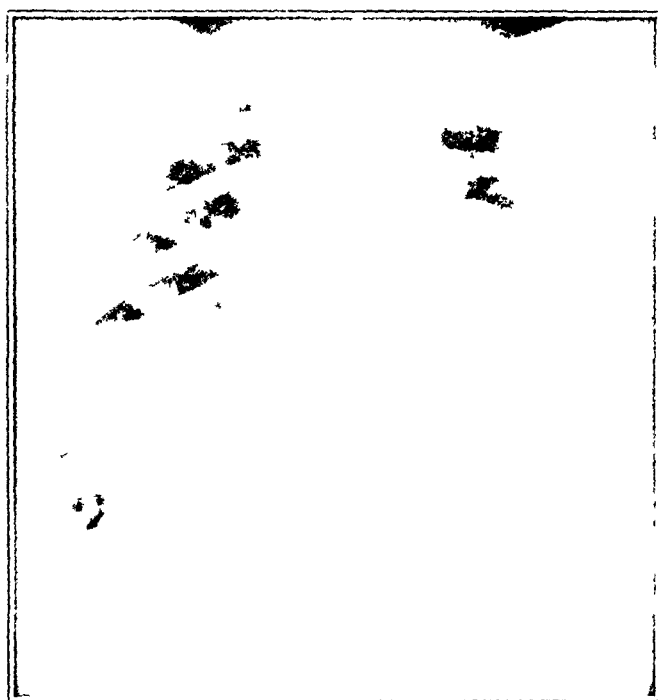


Fig. 16—Periosteal sarcoma, metastases to lungs, with dense lobulated shadows at both bases. A boy aged 18, had a periosteal sarcoma of the left ulna. There was dyspnea, and dulness at the bases of both lungs. From the left side of the chest, 50 cc of bloody fluid was taken. The biopsy report was osteogenic sarcoma. In Hodgkin's disease the shadows are seen higher up, in the regions of the lymph nodes—in the upper mediastinum and the hilums.





Fig 13—Same case as in Figure 12 after eight months' roentgen-ray treatment

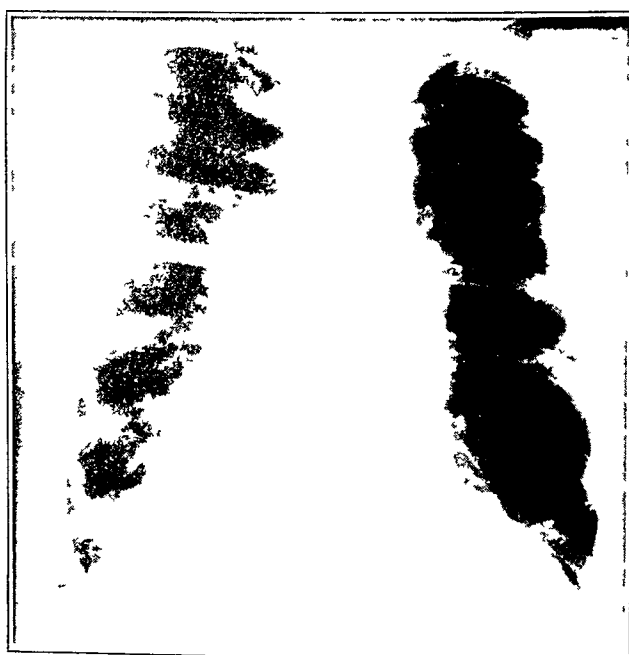


Fig 14—Hodgkin's disease, lobulated shadows at the hilums. A man, aged 32, had night sweats one year before. He lost weight and strength and coughed, but there was little sputum. He had slight dyspnea on exertion. There was no history of exposure to tuberculosis, but he was sent to Arizona. The dyspnea gradually became worse. Physical examination revealed no enlarged nodes in the neck, axillae or groins, and the chest was clear. The temperature, from 100 to 101 F for one week, was reduced by roentgen-ray treatment. The white blood count was 18,000, there were from 73 to 82 per cent polymorphonuclears, 5 per cent lymphocytes and from 12 to 18 per cent large mononuclears. The hemoglobin was 80 per cent. Figure 14 shows definitely lobulated shadows at both hilums.



Fig. 19—Old tuberculosis. The shadows represent calcified areas in the region of the right hilum. The pronounced mottling in the field of the left lung should be compared with Figures 6, 7 and 8.

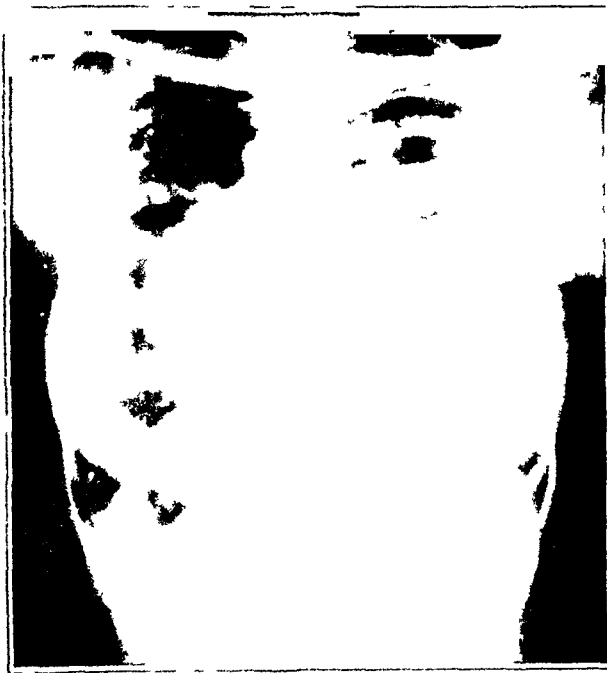


Fig. 20—Tuberculosis with hilum shadows resembling Hodgkin's disease. The case was clinically tuberculosis, the diagnosis not being confirmed by sputum, but owing to the suggestion of lobulation at the hilums in the roentgenogram and the lack of dense areas suggesting calcification, Hodgkin's disease was suspected. The pronounced mottling extending into the field of the right lung, however, together with the fact that the patient was up and about, made a diagnosis of Hodgkin's disease doubtful. Roentgen-ray treatment had no effect on the shadows.



Fig 17—Metastatic carcinoma, dense, homogeneous, sharply outlined, circular and oval shadows in the lung fields. This illustration should be compared with Figure 8, which showed lymphomatous nodules in the lung at necropsy.



Fig 18—Enlarged hilum shadow due to old inflammatory processes. A woman, aged 42, had dyspnea, slightly enlarged lymph nodes in the right side of the neck, paralysis of the left vocal cord and a strongly positive Wassermann test. The biopsy report on a cervical lymph node was tuberculosis or syphilis. A diagnosis of tertiary syphilis was made. The shadow is not definitely lobulated as in Hodgkin's disease.

Owing to definite differences in pathology and the resulting radiographic appearances this can be accomplished in the majority of instances

The most fruitful method of approach to a study of this kind is by an interpretation of the radiographic appearances according to the pathology of the diseases under consideration

show, starts in the glands of the mediastinum or hilus, which grow by expansion and produce lobulations or infiltrations, while tuberculosis in adults at least usually starts in a focus at the periphery of the lung and infects the lymphatics running to the hilus where massive infection takes place

Typically, the radiographic shadows in Hodgkin's disease are confined to the midportion of the chest, while in tuberculosis the mottling often extends all the way to the periphery. In acute and severe cases of Hodgkin's disease, there may rarely be some mottling of the fields of the lung. Owing to fibrosis and calcification, however, the fields of the lung in tuberculosis will show a more pronounced mottling and greater irregularity in density of shadow than in Hodgkin's disease.

In the less common hilus tuberculosis, the process may be confined to this region, but since infiltration tends to occur along the lymphatics, the radiographic shadows tend to streak out radially from the hilus, giving an irregular outline. The shadow varies markedly in density, owing to calcified nodes, caseation and irregular fibrosis.

This picture offers considerable contrast to the rather homogeneous, lobulated shadows with more regular borders seen in Hodgkin's disease.

#### THE ROENTGEN-RAY THERAPEUTIC TEST

One of the most useful methods of differentiating Hodgkin's disease from other conditions, especially carcinoma or tuberculosis, is the roentgen-ray therapeutic test. Blankenhorn<sup>15</sup> considers this to be almost diagnostic. A rapid and marked reduction in the size of the lymphoma is demonstrable by radiograph after one or two treatments, especially if the case is an early one before much fibrosis has taken place in the affected nodes. (Figs 3, 4, 6, 7, 12, 13, 14 and 15 show the effect of roentgen-ray treatment.)

#### CONCLUSIONS

The roentgen ray is a feasible measure to employ as an aid to the diagnosis of Hodgkin's disease because the intrathoracic nodes are often involved in this disease, and the radiographic appearances are fairly characteristic.

In rare cases in which the lymphoma is confined to the thorax and biopsy is not possible, the roentgen ray may greatly aid the diagnosis.

Hodgkin's disease is indicated when the radiograph shows homogeneous, roughly lobulated shadows in the mediastinal or hilus regions, which shrink rapidly under roentgen-ray treatment. Tuberculosis is the most important condition to differentiate from Hodgkin's disease.

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<sup>15</sup> Blankenhorn, M. A. Affections of the Mediastinum, Nelson's Loose Leaf System of Medicine 3 578

of aortic and myocardial invasion in syphilis. A brief selection from the literature indicates the varying frequency with which this condition has been noted.

Gruber<sup>6</sup> in 6 000 necropsy records found aortic syphilis in 4 per cent. Marchand<sup>7</sup> in 256 necropsies on subjects with acquired syphilis found aortic disease in 211 or about 82 per cent. Oberndorfer<sup>8</sup> in 1,436 necropsies on adults found syphilitic aortic disease in ninety-nine cases; in forty the disease was not noted until necropsy. Stadler<sup>9</sup> found aortic involvement in 82 per cent of 156 cases of syphilis in which necropsy had been performed.

Lemann and Mattes<sup>10</sup> studied the heart and aorta of 100 consecutive necropsies. In this series there were three aneurysms. Fifty-five of the 100 showed the aortic changes which have been described as pathognomonic of syphilis; spirochetes were found in the aorta of two cases. Warthin<sup>11</sup> found active lesions in the heart thirty-six times and in the aorta thirty-two times in forty-one cases at necropsy, in twenty-five of these syphilis had not been diagnosed clinically. Lamb's<sup>12</sup> statistics comprise 1 024 necropsies in which forty-seven cases of aortitis were noted; ten of these were aneurysms. Syphilitic aortitis represented 14.56 per cent of the cardiac cases which included heart conditions secondary to nephritis and hypertension. Hubert<sup>13</sup> stated that aortitis comprised 70 per cent of all cases of visceral syphilis and 14.6 per cent of syphilis in general.

The Wassermann test has been found to yield a large proportion of positive reactions in cases diagnosed as aortitis. Citron<sup>14</sup> elicited a positive Wassermann reaction in 60 per cent of cases of aortic insufficiency. Of seventy-one marked cases of aortic syphilis Oberndorfer<sup>8</sup> reported a positive Wassermann reaction in sixty-seven. Pearce<sup>15</sup> collected seventy cases of aortitis from the literature, in 78.5 per cent of which the Wassermann reaction was positive. Eich<sup>16</sup> elicited a positive reaction in 81.8 per cent of forty-four cases which showed characteristic syphilitic aortic disease at necropsy, but in some instances post-mortem blood was used in the test, which renders the results doubtful.

6 Gruber, G. B. Ueber die Doehle-Heller'sche Aortitis, Jena, 1914.

7 Marchand. Verhandl. d. deutsch. path. Gesellsch. **6** 137, 1903.

8 Oberndorfer. Munchen med. Wehnschr. **60** 505 (March) 1913.

9 Stadler. Syphilitic Aortenerkrankung, G. Fischer, Jena, 1912.

10 Lemann, I. I. and Mattes, A. South M. J. Sept., 1920, p. 623.

11 Warthin, S. Am. J. M. Sc. **152** 508 (Oct.) 1916.

12 Lamb, A. R. Nelson's Living Medicine, New York, F. Nelson, **4**, 1920.

13 Hubert, G. Deutsch. Arch. f. klin. Med. **128** 317 (Feb.) 1919.

14 Citron, J. Berl. klin. Wehnschr. **45** 2142 (Nov.) 1908.

15 Pearce, R. M. The Wassermann Reaction in the Pathology, Diagnosis and Treatment of Syphilis, Arch. Int. Med. **6** 478 (Nov.) 1910.

16 Eich, P. Frankfurter Ztschr. f. Path. **7** 373, 1911.

# CLINICAL AND ROENTGENOLOGIC STUDY OF ONE HUNDRED AND FIVE CASES OF SYPHILIS WITH REFERENCE TO THE CARDIOVASCULAR SYSTEM \*

EDWARD STEINFELD, M D, GEORGE E PFAHLER, M D

AND

JOSEPH V KLAUDER, M D

PHILADELPHIA

This paper concerns itself with the clinical and roentgenologic study of 105 patients known to be syphilitic, with particular reference to the presence of cardiovascular disease. The association of central nervous involvement with aortic disease and the specific treatment of aortic syphilis were considered to be not without interest. The roentgenologic evidence of aortic syphilis in particular is treated in an additional section by Dr Pfahler.

The study of cardiovascular disease in syphilis received its impetus particularly by the recognition of a characteristic and frequent aortic involvement. Although the earliest systematic description of aortic syphilis is ascribed to Doehle,<sup>1</sup> and Heller,<sup>2</sup> their efforts were anticipated by Francis H. Welch<sup>3</sup> who, in November, 1875, read a paper on 117 cases of aortitis, in 46 per cent of which there was a clear record of syphilis. He also reported a series of fifty-six cases of fatal syphilis, of which thirty-four presented aortic lesions. Another early contribution is that of Heiberg,<sup>4</sup> who, in Christiania, in 1876, reported on the relation of aneurysm and arterial disease to syphilis. Kreftings<sup>5</sup> has called attention to this record. Since this time an ever increasing literature has testified to the growing interest and understanding of this subject. In recent times, the earlier recognition of aortitis has been facilitated by accurate complement-fixation tests for syphilis and by roentgenologic methods. These methods of precision and the testimony of former and recent pathologic studies have revealed a high incidence

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\* From the Department of Dermatology and Syphilology, clinic of Dr Jay F. Schamberg and the medical clinic of Dr R. Max Goepp, Graduate School of Medicine, University of Pennsylvania.

\* Roentgenologic study aided by a grant from the Research Institute of Cutaneous Medicine.

1 Doehle. Inaug. Diss., Kiel, 1885, *Deutsch. Arch. f. klin. Med.* **55** 190, 1895.

2 Heller, A. *Verhandl. d. deutsch. path. Gesellsch.*, vol 2, 1899.

3 Welch, F. H. *Med.-Chir. Trans. Ser. 2*, vol 41, 1876.

4 Heiberg, H. *Norsk Mag. f. Laegevidensk.* **6** 55, 1876.

5 Kreftings, R. *Berl. klin. Wchnschr.* **47** 713, 1910.

the intima and there are numbers of isolated or confluent grayish translucent or yellowish nodular areas, some of which have cicatricial puckering in the center. Unless there is a secondary deposit of calcareous material, the lesions do not resemble the areas of calcified plaques nor ulcerations usually seen in the more distal portions of the aorta in atheroma. The walls of the affected portion of the aorta are thinned out in places with small aneurysmal pouchings. There is often thickening and shrinking of the aortic valves and narrowing around the mouths of the coronary vessels. The ascending aorta may be uniformly dilated, with involvement of the aortic valves. This type of diffuse aortic dilatation was described as early as 1815 by Hodgson<sup>28</sup> and is systematically described in its relation to syphilis by McCrae.<sup>29</sup>

Microscopically the lesions are seen to be inflammatory and not of a degenerative character as in atheroma. There are areas of infiltration about the vasa vasorum in the adventitia and media with lymphoid cells, plasma cells and giant cells; there is fragmentation of the elastic tissue with replacement by fibrous tissue containing wandering cells. The intima may show a thickened fibrous change, but there is little fat or calcium deposit as in atheroma. The peri-adventitial lymph nodes have been noted to be enlarged in conjunction with these lesions. The predilection of the spirochete for the proximal aorta has been explained by Klotz<sup>27</sup> to be due probably to the rich network of lymphatics draining the outer wall of the aorta and communicating with large lymph channels. Though it is argued by some observers that the predilection for the lymphatic drainage bed in the thorax remains to be explained it appears to be an important observation.

#### SYMPTOMATOLOGY

The symptoms of aortic syphilis are thoracic pain—usually substernal or precordial—dyspnea, palpitation of the heart, cough, changes in voice, weakness, edema of the ankles and sometimes loss in weight. The thoracic pain may take on the characteristics of a true angina with radiation of pain down the left arm, or may be complained of as merely a sense of oppression in the chest. The dyspnea may in some cases be of a paroxysmal nature. It is of vital importance that cardiac syphilis be diagnosed at the earliest possible time. When one considers the long period between the time when the heart and aorta are invaded to the frank development of subjective and objective symptoms, it becomes apparent that comparatively minor signs are sufficient to warrant a presumptive diagnosis. These early signs may be confined to some tenderness over the manubrium, a systolic murmur at the aortic area

28 Hodgson, J. A Treatise on the Diseases of the Arteries and Veins, London, 1815.

29 Klotz, O. Am J M Sc 155 92 (Jan.) 1918.



In a study of thirty-six cases of aortic disease, Cummer and Dexter<sup>17</sup> found a positive Wassermann reaction in twenty-seven, or 75 per cent. Of forty-seven cases examined by Longcope,<sup>18</sup> thirty-five or 74.4 per cent gave a positive reaction. Schotmuller<sup>19</sup> in 189 patients with positive Wassermann reactions, found aortitis twenty-eight times. Hubert<sup>13</sup> studied 220 patients with syphilitic aortitis, in 85 per cent of 186 cases, the Wassermann reaction was positive. Brown<sup>20</sup> noted seven cases of aortitis in 136 patients giving a positive Wassermann reaction.

The presence of the spirochete in the diseased aorta furnished a striking demonstration of its etiologic significance. Reuter,<sup>21</sup> in 1906, described the finding of the spirochete in the wall of the affected aorta. Benda,<sup>22</sup> Schmorl<sup>23</sup> and Wright and Richardson<sup>24</sup> also demonstrated the spirochete in the heart and aorta of syphilitic persons. Larkin and Levy<sup>25</sup> considered the demonstration of spirochetes in these lesions as doubtful, and Longcope stated they could not be demonstrated constantly. Warthin,<sup>26</sup> in 1911, found the heart wall crowded with spirochetes in congenital syphilis in nine infants and young children who came to necropsy. In later publications he emphasized the persistence of the organism in the heart and aorta of patients free from symptoms.

The clinical features of the disease were reviewed by Longcope<sup>18</sup> in 1913 in a comprehensive article based on the study of sixty-three patients of which twenty were treated with arsphenamin. The systematic description of aortic dilatation was given by McCrae,<sup>27</sup> who noted a definite proportion of these cases to be due to syphilis.

#### PATHOLOGY OF AORTITIS

Grossly, there are a number of characteristics which distinguish the syphilitic aorta from the plaques of simple atheroma. The changes in syphilitic aortitis usually appear near and above the valves (supra-aortic) and tend to spread upward along the transverse arch and down to the aortic leaflets. There is a wrinkled appearance of

17 Cummer, C. L., and Dexter, R. D. The Relation of Aortitis to Syphilis, and the Importance of Its Recognition, *J. A. M. A.* **59** 419 (Aug. 10) 1912.

18 Longcope, W. T. Syphilitic Aortitis. Its Diagnosis and Treatment, *Arch. Int. Med.* **11** 15 (Jan.) 1913.

19 Schotmuller, quoted by A. R. Lamb. *Nelson's Living Medicine*, **4** 533.

20 Brown, G. E. *Am. J. M. Sc.* **157** 41 (Jan.) 1919.

21 Reuter. *Munchen med. Wchnschr.* **53** 778 1906.

22 Benda. *Berl. klin. Wchnschr.* **43** 989 1906.

23 Schmorl. *Munchen med. Wchnschr.* **54** 188, 1907.

24 Wright, J. H., and Richardson, O. *Boston M. & S. J.* **160** 539, 1909.

25 Larkin, J. H., and Levy, I. J. *J. Exper. M.* **23** 25 (Jan.) 1916.

26 Warthin, A. S. *Am. J. M. Sc.* **141** 398 (March) 1911.

27 McCrae, T. *Am. J. M. Sc.* **140** 469 (Oct.) 1910.

We have not assumed that the number of aortic cases represents the true proportion of definite lesions among a group of syphilitic persons due to the fact that a number of these patients were recognized to have aortic disease in medical clinics and were therefore included when the Wassermann reaction was reported to be positive.

#### 'WASSERMANN-FAST' SYPHILIS AND CARDIAC SYPHILIS

The statement has frequently appeared in the literature that syphilitic patients with persistently positive Wassermann reactions are particularly likely to have cardiac syphilis or neurosyphilis. This has not been in strict accord with our experience. The term 'Wassermann-fast,' it appears, has been used without discrimination; it has no definite significance but only a relative one, since it implies a Wassermann reaction which remains positive in spite of treatment to what amount of treatment would be variably stated by different observers. We have heard it used in reference to a positive reaction after as few as fifteen injections of neosphenamin, others apply the term to those cases in which the reaction is positive in spite of a considerable number of injections—fifty or more. As a matter of fact the greater the amount of treatment the less percentage of 'Wassermann-fast' reactions will be observed. It is, therefore, desirable to qualify the term 'Wassermann-fast' by stating to what amount of treatment the reaction is persistently positive.

We have observed many syphilitic patients whose Wassermann reaction was persistently positive in spite of considerable antisypilitic therapy, in whom no cardiac involvement or neurosyphilis could be clinically demonstrated. Perhaps the best example of this group is represented in the subject of congenital syphilis in whom the Wassermann test notably remains positive in spite of treatment. It is not our purpose to discuss the 'Wassermann-fast' case so far as neurosyphilis is concerned, but it may be stated that, excluding paresis, it is not uncommon to observe a negative blood Wassermann reaction in patients with neurosyphilis.

#### ARTERIAL THROMBOSIS

The picture of syphilitic disease of the peripheral arteries represents the same process as that in the large vessels. It has been noted universally that arterial thickening, especially when occurring prematurely, is a prominent feature of this infection. Indeed, this factor in the causation of arteriosclerosis was being overemphasized until the studies of Thayer,<sup>31</sup> Klotz,<sup>32</sup> and others demonstrated that many infections

31 Thayer, W. S. *Am J M Sc* **127** 391 (March) 1904.

32 Klotz, O. *Arteriosclerosis*, Lancaster, New Tra Pub. Co., 1911.

and an accentuated wooden-like aortic second sound. In the stage of dilatation, however, the signs are numerous. Pulsations are noted in the carotid arteries, in the suprasternal notch, subclavian arteries and sometimes in the second and third interspaces on either side of the sternum. The veins are prominent over the chest and at times suffusion of the tissues above the clavicle is noted. The pulsation of the right subclavian artery becomes easily palpable. There is increased supracardiac dulness, and a systolic murmur is commonly heard at the aortic area and transmitted to the carotids. The aortic second sound takes on a peculiar accentuated mellow sound likened by Allbutt<sup>30</sup> to the "tabourka" or Algerian drum and described by McCrae as a wooden bell-like note. If there is aortic insufficiency, a diastolic murmur is noted and is heard best along the edge of the sternum. The well known collapsing type of pulse is characteristic at this stage. The cardiac impulse is extended downward and to the left.

With a sacculated aneurysmal dilatation there are noted in varying degree the added signs of mediastinal pressure, difference in pulses, tracheal tugging, inequality of the pupils, hoarseness, aphonia or brassy cough. If the lesion is in the ascending arch, a pulsating tumor may present itself in the upper part of the chest.

#### INCIDENCE OF AORTIC AND MYOCARDIAL DISEASE IN 105 SYPHILITIC PATIENTS

Male patients only were studied, of these, sixty were white and forty-five were negroes. They varied in age from 22 to 59 years and the duration of syphilitic infection varied from one to twenty or more years. Approximately, one-fourth were between 40 and 50 years of age. In establishing a clinical diagnosis of aortitis, a sufficient number of the signs and symptoms described above were elicited before the patient was considered to present well-defined aortic disease. The association of corroborative evidence by roentgenoscopy was noted. Of the 105 patients, twelve were found to be suffering from aortic or myocardial disease. Of these, three were white and nine were negroes. Of the aortic lesions, one was diagnosed as aortitis, two as aortic dilatation, six as aortic dilatation and insufficiency and two as aneurysm. A brief outline of the histories of some of these patients is given under the heading of treatment. The ages of 11 of these patients ranged from 37 to 57 years, the comparatively early appearance of aortic insufficiency in the twelfth patient at the age of 30 is explained by the fact that infection occurred at the age of 15. The Wassermann reaction was four plus in all these patients except one with aortic dilatation, in whom the reaction was plus three.

30. Allbutt, Sir T. C. *Disease of the Arteries*. London, Macmillan Co., 1915.

1879, described the association of tabes and aortic insufficiency. Fournier<sup>35</sup>, Grasset<sup>36</sup> and Letulle<sup>37</sup> were of the impression that aortic disease was rare in tabes. Charcot<sup>38</sup> and Vulpien,<sup>39</sup> particularly, considered the association relatively frequent. Ruge and Huttner<sup>40</sup> found nine cases of aortic insufficiency among 138 tabetic patients. Nordman<sup>41</sup> reported eight cases of aortitis among 100 tabetic persons. Hertz,<sup>42</sup> in ninety-eight cases of tabes, noted six cases of aortic insufficiency, two of aneurysm and sixteen cases of aortic dilatation, while in another series he found forty-eight cases of aortic insufficiency among seventy-six tabetic persons. Hubert<sup>43</sup> found tabes in 25 per cent of 220 cases of aortitis. Guilly<sup>44</sup> in 200 patients with paresis found evidences of aortic disease at necropsy in forty-one. A recent and comprehensive report of this question by Friedman<sup>45</sup> gives the results of a similar study in three series. In one series of fifty cases of tabes, he noted seven patients with cardiovascular disease. In the second series of forty cases of neurosyphilis, there were seven instances of cardiovascular involvement. In the third series derived from postmortem records of the State Hospital for the Insane at Morristown, N. J., 1907 to 1915, he selected eighty-three cases of paresis in patients about 45 years of age or less, in this group he found forty-nine with changes in the aorta indicative of syphilis and also similar changes in thirteen of the older patients, making a total of sixty-three cases in which there was aortic disease, or 75 per cent.

Although the small number of patients with neurosyphilis in our own series precludes the attachment of much significance to a similar analysis, we can record one marked case of aortic insufficiency among five patients with paresis and three cases of widening of the ascending arch of the aorta in another group of twenty patients with neurosyphilis, of whom eleven were tabetic patients. From these figures we cannot infer any unusual frequency or rarity of the coexistence of these two types of syphilitic involvement. It may be of significance to note, however, that in the patients presenting marked and severe cardio-

35 Fournier. *Traité de la Syphilis*, 1899.

36 Grasset, quoted by Bouvieret. *Lyons med.* **13**, 235, 1885.

37 Letulle. *Gaz. med. de Paris* **39-40**, 504, 1880. *Presse med.* **4**, 605, 1896.

38 Charcot, quoted by Friedman. On the Associated Incidence of Syphilis of the Central Nervous System and Cardiovascular Syphilis, *Arch. Neurol. & Psychiat.* **1**, 289 (March) 1919.

39 Vulpien. *Mal. du Syst. Nerveux*, 377, 1889.

40 Ruge and Huttner. *Berl. klin. Wchnschr.* **34**, 760, 1897.

41 Nordman. *Le cœur de tabétique*, Theses de Paris, 1895.

42 Hertz. *Les nerfs du cœur chez les tabétiques*, Theses de Paris, 1903.

43 Guilly. Theses de Paris, No. 57, 1904-1905.

44 Friedman, E. D. On the Associated Incidence of Syphilis of the Central Nervous System and Cardiovascular Syphilis, *Arch. Neurol. Psychiat.* **1**, 289 (March) 1919.

(notably typhoid fever) are prone to inflict injuries on the artery, resulting in noticeable thickening. In ascribing any radial thickening in a series similar to the one under discussion, it is obviously advisable to rule out if possible the factors of hypertension, infections other than syphilis, chemical poisons and the degenerative atherosclerosis termed "decreascent arteriosclerosis" by Allbutt. With these exceptions in mind, there were noted sixteen patients of the total number of 105 who presented changes varying from arterial thickening to marked sclerosis. Twelve were in an age period in which decreascent atherosclerosis would be unlikely. It is a familiar observation that changes may occur in peripheral or cerebral arteries without clinically demonstrable lesions in the aorta. Conversely, aortic lesions are noted without concomitant changes in the radials. However, in this series, seven of the eleven patients with known aortic cases presented radials varying from definite thickening to actual sclerosis.

#### BLOOD PRESSURE

Syphilis apparently plays no part in the common type of vascular hypertension (hyperpiesia), especially of the climacteric group. In the present series of 105 patients hypertension ranging from 180 to 200 mm of mercury, systolic pressure, was noted only seven times. It appears that a slight rise in pressure was present in some of the patients showing aortic lesions with, however, a marked amplitude of pulse pressure in the patients with aortic insufficiency. Whether the added vascular tension predisposed to aortic changes or was a manifestation of the lesion seemed to be a question for each individual case.

A definite state of lowered pressure, especially when the age period is considered, existed in thirty cases, or nearly one third of the total number. Fifteen of these thirty patients had systolic pressure at 100 mm of mercury or below. Demetre<sup>33</sup> has recorded a state of lowered arterial tension in tabes, although the figures given in this table fall into a range which we have considered might be noted in normal cases. In one third of thirty patients with neurosyphilis in the present series, the arterial tension was below a systolic pressure of 120. It is possible that vascular hypotension is an index of the asthenia noted in some of the patients suffering from tabes.

#### ASSOCIATION OF THE AORTIC DISEASE AND NEUROSYPHILIS

The association of aortic involvement with neurosyphilis has been noted by various observers, although they have not been in accord as to the frequency of this coincidence. Berger and Rosenbach,<sup>34</sup> in

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33 Demetre, M. P. Bull. et mem. Soc. med. de hop. de Paris 9:349 (March 17) 1921.

34 Berger and Rosenbach. Berl. klin. Wchnschr. 27:402, 1879.

If the patient was doing well he was admitted for observation during the period of arsphenamin treatment. Minimal doses of 0.1 or 0.2 gm. neo-arsphenamin increased up to 0.3 or 0.4 gm. (and up to 0.6 gm. in the favorable cases) were given once or twice a week. After about six to ten injections improvement was sufficiently noticeable and the person continued the treatment as an ambulatory patient. Digitalis was given when indicated. At times striking changes in the subjective symptoms were noted. Dyspnea, pain and cough were usually relieved, and the disability of the patient was lessened. The duration of the arsphenamin treatment was not constant in all cases, frequently owing to the fact that the patients after amelioration of symptoms were apt to stay away from the clinic.

However, the aim has been to continue the use of mercurials in between series of arsphenamin injections. The use of intramuscular injections of mercuric succinimid or subvalate at weekly intervals is of value. As a rule physical signs remain practically unchanged even in the face of subjective improvement, although at times pulsations in the neck and to the sides of the sternum may grow less. The characteristic results in some of the patients suffering from well advanced aortic disease are noted in brief outlines.

#### ROENTGENOLOGIC STUDIES

*Roentgenologic Evidence of Syphilitic Aortitis.* Assman<sup>49</sup> gives these causes of enlargement of the aorta: (1) old age—physiology, (2) atheromatosis, (3) syphilitic aortitis and (4) cardiac disease. (a) in nephritis—due to high blood pressure, (b) aortic insufficiency and (c) isthmus stenosis of the aorta.

He says that in middle age with no cardiac lesion and no high blood pressure one should consider syphilitic aortitis. In twenty-seven cases proved by necropsy the width of the aortic shadow was approximately 5.5 cm. as compared with the normal about 3.5 cm.

The two leading signs of syphilitic aortitis are dilatation in the first portion and abnormal pulsation. The dilatation may be local or diffuse, with diffuse dilatation the density is increased. If calcification has taken place dense plaques may be seen.

Increased pulsation is due to high blood pressure, aortic insufficiency and stenosis at the isthmus and to thinning of the walls in syphilitic

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At the present time the term "Hersheimer" reaction is used in a still more general way than Nersser's "general" reaction. It is given as the explanation of the provocative Wassermann reaction. It is used to explain local reactions other than in the original sense, for instance a rupture of an aneurysm following the administration of arsphenamin, etc. Mercury is a less powerful spirocheticide than is arsphenamin and is, therefore, less likely to produce a Hersheimer reaction.

<sup>49</sup> Assman. Die Klinische Roentgendagnostik der Inneren Erkrankungen, Leipzig: Vogel, p. 115.

vascular involvement, neurosyphilis was noted only once, whereas the total number of patients with neurosyphilis comprised nearly one fourth of the total series

There is a well-known dogma to the effect that syphilitic patients rarely present clinical manifestations of tertiary syphilis involving different systems. This statement holds true in the majority of patients with tertiary syphilis whom we have examined. It is not uncommon, however, to observe syphilitic patients with active tertiary manifestations, who also present one or more neurologic abnormalities, a normal spinal fluid and the absence of subjective symptoms of neurosyphilis. These findings in all likelihood represent a scar of a former neurologic process. It appears that syphilis in the majority of cases is expended in only one system of the body. The work of Warthin, however, has shown that pathologically this is the exception rather than the rule. It can appropriately be recalled here that those who advocate the existence of separate strains of spirochaetes point to the aforementioned dictum in support of their theory.

#### TREATMENT

The favorable effect of specific treatment on aortic syphilis in all its stages has been noted in most of the writings on this subject. Without reviewing the considerable literature on this phase of the subject, the recent reports of Elliott<sup>45</sup> in particular, are of interest. Also MacLachlan<sup>46</sup> has recently reported good results in a small series of patients with aneurysm by the use of arsphenamin combined with rest, diet and other medical measures. In order to avoid untoward effects we start treatment with mercury in the form ofunctions or the yellow mercurous iodid by mouth, for a period of six weeks. The possibility of a Herxheimer reaction,<sup>47</sup> which may occur after an initial injection of arsphenamin, is also rendered less likely by this procedure. We can appropriately mention the following observation.

Some years ago a patient with an aneurysm previously untreated was given a full dose of arsphenamin. Within the following twenty-four hours death suddenly ensued, necropsy revealed a ruptured aneurysm. This occurrence has been properly called a local Herxheimer reaction<sup>48</sup>

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45 Elliott, A. R. *Am J M Sc* **154** 14 (July) 1917, *Med Clin of North America* **1** 1305 (March) 1918.

46 MacLachlan, W. W. G. *Am J M Sc* **159** 525 (April) 1920.

47 Herxheimer and Krause. *Deutsch med Wchnschr* **27** 895, 1902.

48 In the treatment of secondary syphilis with arsphenamin, the phenomenon of the Jarisch-Herxheimer reaction is observed. This reaction, as originally described, was a local one—an accentuation, reddening and swelling of the macular and papular rashes occurring within twenty-four hours after the use of mercury. Besides this "local" reaction, Neisser mentions a general one after treatment with arsphenamin which is characterized by transitory increase of the headache in cerebral syphilis and of the lightning pains in tabes.

aortitis Even in syphilitic aortitis with diffuse dilatation there is apt to be some localized dilatation also, especially immediately above the aortic valves

Elliott <sup>45</sup> says "Of all the methods of diagnosis to determine the presence of aortic disease, the roentgen ray is the most valuable"

In aortitis, the roentgen ray reveals two kinds of changes alterations in density of shadow and changes in contour In early aortitis,



Fig 1—An oblique view showing well marked dilatation of the first portion of the arch

the pathologic process is confined to the origin of the aorta As the vessel at this stage is not thickened and no lime salts exist, there may be merely a slight dilatation of the first part of the arch, with exaggerated pulsation at that point

Some dilatation of the aorta is quite common in aortic sclerosis, but this is likely to affect the entire aorta, and the entire aortic shadow is increased





Holmes and Ruggles<sup>50</sup> say "A marked prominence of the aortic shadow to the right is almost always due to specific aortitis"

McGraven and Scott<sup>51</sup> argue that since the cardiovascular system is the most frequent and vulnerable point of attack for the spirochetes, every syphilitic patient should be suspected of having aortic or cardiac involvement. Levison says, "The earliest x-ray evidence should be looked for at a point where pathological lesions are most common, that is, just above the semilunar valves in the suprasigmoid part of the aorta"

Our observations have been based on the study by fluoroscope and teleoroentgenograms made at a distance of 2 meters, and oblique films in sixty-three patients who were known to be syphilitic. We found that the age ranged from 20 to 25 in eight cases, from 25 to 30 in nine cases, from 30 to 35 in thirteen cases, from 35 to 40 in eight cases, from 40 to 45 in four cases, from 45 to 50 in eight cases, from 50 to 55 in eleven cases and from 55 to 60 in two cases. The roentgenograms showed that the heart and aorta were normal in twenty-three cases, probable aortitis in nineteen cases, syphilitic aortitis in eighteen cases and aneurysm in three cases—of the first portion in one case, of the arch in one case and of the descending portion in one case.

The cases classed as probable syphilitic aortitis showed the roentgenologic evidence of aortitis, but had associated cardiac disease, hypertension, or were not quite characteristic. However, since the pathologic reports on similar cases give a high percentage of positive diagnoses of syphilitic aortitis, it is quite likely that this doubtful group should be counted as positive. However, excluding these, the figures would then give syphilitic aortitis in 28.5 per cent and aneurysm in 4.7 per cent of our cases.

These conditions were found in the lungs: pulmonary syphilis in one case, probable pulmonary syphilis in five cases, normal lungs in forty-two cases, probable tuberculosis in one case, calcified bodies in two cases. The condition in twelve cases was not reported.

It would seem from these studies that it is important to make a careful roentgenologic study in every patient with syphilis who has any chest symptoms, no matter how slight.

#### REPORT OF CASES

CASE 1—J. S., a negro, aged 52 years, had an initial lesion at the age of 26. The present complaints were substernal pain, dyspnea, cardiac palpitation and cough. The supracardiac dulness was widened to percussion, and a double aortic murmur was heard, the diastolic element of which was well transmitted down the left border of the sternum. There was moderate left-sided hyper-

50 Holmes, G. W., and Ruggles, H. E. *Roentgen Interpretation*, Philadelphia, Lea and Febiger, 1921.

51 McGraven and Scott. *Ohio State M. J.* 18:477 (July) 1922.

In aortic dilatation due to high blood pressure, there is likely to be associated hypertrophy of the left ventricle. In early aortitis there is no enlargement of the heart unless there is an associated valve defect or hypertension. In aortitis, the aortic shadow is likely to increase to the right above the shadow of the right auricle.

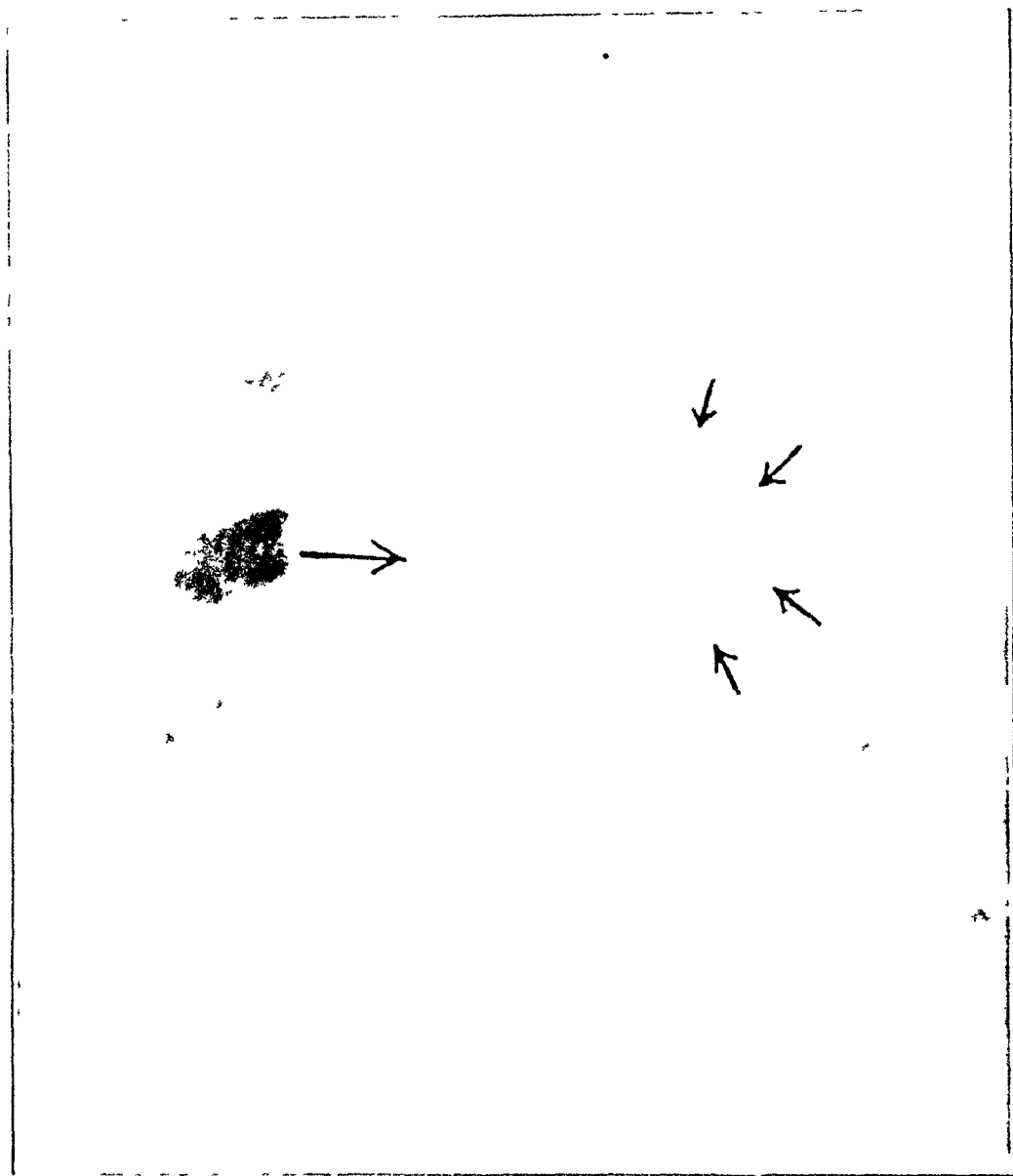


Fig. 2—Moderate dilatation of the first portion of the arch on the right and an abnormal mass at the root of the left lung, probably a gumma.

If the disease involves the entire arch, one must expect a dilatation of the entire arch, with a total increase in the width, but one is not likely to have the buckling or knob observed as the result of the elongation which occurs in arteriosclerosis. If the disease extends to the innominate or common carotid, these vessels are likely to be dilated and give increased shadows.

The blood Wassermann test was + + + + Management similar to that in the foregoing cases produced some amelioration of symptoms After going about his work a return of his symptoms was noted, but on continued mercurial, arsphenamin and digitalis medication, he remained fairly comfortable

#### SUMMARY

A brief review of the literature on cardiovascular syphilis is made The pathology of syphilitic aortitis is discussed

The symptomatology of syphilitic aortitis is presented with particular reference to early symptoms The importance of an early diagnosis is emphasized

Of a group of 105 male syphilitic patients studied by clinical methods, sixty were white and forty-five were negroes They varied in age from 22 to 59 years, and the duration of syphilitic infection varied from one to twenty or more years Approximately, one fourth were between 40 and 50 years of age Twelve patients, approximately 10 per cent, were found to be suffering from aortic or myocardial disease Of these, three were white and nine were negroes Of the aortic lesions, one was diagnosed as aortitis, two as aortic dilatation, six as aortic dilatation and insufficiency and two as aneurysm

Of sixty-three patients studied by roentgenologic methods, aortic disease (including aneurysm) was noted as being definitely present in nineteen, or 33 per cent Roentgenologic examination included fluoroscopy, teleroentgenograms made at a distance of 2 meters and oblique films The higher percentage of patients with aortic disease discovered by roentgenologic examination is in accord with pathologic studies reported by others and reviewed in this report

The so-called Wassermann-fast syphilitic patient is discussed with particular reference to cardiac syphilis

Of a total number of twenty-five patients with neurosyphilis, there was an associated aortic disease in four The relative infrequency of an active syphilitic process involving one or more systems in the same patient is discussed

trophy. The blood pressure was systolic, 115, diastolic, 25. The blood Wassermann test was + + + +. The roentgen ray and fluoroscope showed widening of the aorta and left-sided hypertrophy. After preliminary trial with yellow mercurous iodid and moderate doses of digitalis, he received injections of neo-arsphenamin in graded dosage up to 0.6 gm.

Amelioration of the cough, dyspnea and pain was noted after three or four injections. One year after treatment, he reported no return of his symptoms.

CASE 2—J. F., a negro, aged 30 years, gave a history of a chancre at the age of 15. When first seen he was suffering with dyspnea of six months' duration, with orthopnea for the past three months. Cough and soreness over the precordium had been noted, and he had been unable to work for about five months. The examination, in brief, revealed marked pulsations of the carotids, aortic dilatation with insufficiency and increased size of the heart. The fluoroscope outlined a dilated ascending aorta and the teleroentgenographic measurements were: right base, 7 cm., left base, 6 cm., aortic area, 7 cm., the cardiothoracic ratio was 73 per cent.

The blood Wassermann was + + + +. The blood pressure was systolic, 120, diastolic, 40, showing the characteristic amplitude of pulse pressure. After preliminary treatment with mercurous iodid test and digitalis, he received, while under observation in the ward, a series of six intravenous injections of neo-arsphenamin, starting with 0.2 gm. and increasing to 0.5 gm. He then continued the injections from the outpatient department for six more doses. There was marked subjective improvement which persisted up to six months, despite the fact that he was in another city most of this time.

CASE 3—P. G., a negro, aged 37 years, could give no definite statement as to duration of disease. He complained of substernal pain radiating down the left arm, dyspnea, marked palpitation and cough. Examination revealed marked pulsations in the neck, particularly of the right carotid, increase in supracardiac dulness, wooden-bell-like aortic second sound and a short aortic systolic murmur. The blood pressure was systolic, 150, diastolic, 100. The signs indicated aortic dilatation, but nothing indicative of aortic insufficiency. Roentgenoscopy showed dilatation of the ascending arch of the aorta. Under a regimen much as outlined in the first two cases, he noted marked lessening of pain, cough and dyspnea. The improvement was known to have persisted for at least nine months.

CASE 4—B. S., a negro laborer, aged 52 years, had had an mitral lesion at the age of 19. For the past two years he had complained of persistent substernal pain, dyspnea and inaudible wheezing in the chest. He noticed dysphagia at times. Examination and roentgenoscopy revealed a large aneurysm of the ascending aorta. The blood Wassermann reaction was 4 plus. The treatment was similar to that in preceding cases, the highest dose of neo-arsphenamin being 0.4 gm. There was noticeable amelioration of pain and dyspnea, and against advice the patient went back to laboring work. He returned in several months with most of the original complaints, but with rest, digitalis medication and six injections of neo-arsphenamin, he improved sufficiently to undertake light work.

CASE 5—C. E., a negro, aged 42, had a doubtful history of chancre at the age of 18. He had never received treatment and complained at first observation of cough, dyspnea and pain down the left arm. There was sclerosis of the peripheral arteries, and heaving pulsations were noted in the carotid and subclavian arteries. The supracardiac dulness measured 8 cm. The teleroentgenographic measurements were: heart length, 19.2 cm., right base, 6.2 cm., left base, 6.0 cm., heart width, 18.8 cm., aortic area, 4.7 cm. to the right and 4.2 cm. to the left. The cardiothoracic ratio was 73 per cent, indicating marked increase of cardiac outline. A systolic and diastolic murmur was noted over the aortic area, a mitral systolic murmur probably due to relative insufficiency was also noted. The blood pressure was systolic, 185, diastolic, 85.

for and against the influenza bacillus as the causative agent. No attempt will be made to make a summary of these points or to refer to all the publications on the subject. Attention is called to the recent publications by McIntosh<sup>8</sup> with their complete list of references.

It is at the present time an unsettled point whether lung involvement is due to the virus of the epidemic disease or is dependent on some secondary invading organism. However, it is agreed by all that no matter what the etiology of the epidemic may be, it renders the lower respiratory tract susceptible to invasion by other organisms. As involvement of the upper respiratory tract and bronchi in this disease with productions of characteristic sputum is generally conceded, and as special pulmonary lesions have been pointed out by Goodpasture,<sup>2</sup> Wolbach<sup>7</sup> and others, that are not seen in other inflammatory conditions of the lungs, it seems reasonable to assert that the virus of this epidemic disease will cause pulmonary lesions in some cases without the presence of complicating organisms. That important pulmonary lesions do not occur in the majority of cases has been established by the clinical course of the disease, for during the epidemic the large majority of the cases ran the course of a self-limited acute febrile infection without signs suggestive of a lung involvement. However, in a considerable percentage of cases, about 25 per cent, the process extends from the bronchi into the lung tissue. It is unlikely that this disease results fatally without pulmonary involvement.

Although this study failed to establish the cause of the epidemic, it brought out certain points in regard to the relationship between the various bacteria present and the epidemic disease, so that a discussion of the etiology of this disease has been included. For example, in this study certain pulmonary lesions have been found which are considered characteristic of this epidemic disease. These lesions were present in all but one of the cases studied, and yet in this group there was no one bacterium always present. In the one case in which the characteristic pulmonary lesions were not found, death did not occur until over four weeks after the onset of the disease, and the early lesions in the lungs had been replaced and obscured by secondary infections and repair. The influenza bacillus was found more frequently than any other bacterium, and yet it was not recovered by culture or found in the sections<sup>9</sup> of the lungs in a small percentage of the cases. Furthermore in one instance in which this peculiar pulmonary reaction was found in the uncomplicated state, no bacteria could be demonstrated at the site of these characteristic pulmonary lesions. The inconstancy of the presence

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8 McIntosh, J. Studies in the Etiology of Epidemic Influenza. Special Report, Series 63. Privy Council, Medical Research Council, 1922.

9 In this study, bacteria were looked for in sections which were prepared with the Giemsa stain.

# THE INFLUENZA EPIDEMIC AT CAMP DEVENS IN 1918

A STUDY OF THE PATHOLOGY OF THE FATAL CASES \*

S BURI WOLBACH M D

AND

CHANNING FROTHINGHAM, M D

BOSTON

It may arouse wonder that another contribution to this much discussed subject should be offered so long after the subsidence of the pandemic form of this disease in view of the excellent reports on the pathology of the disease already presented by numerous investigators, including Goodpasture and Burnett,<sup>1</sup> Goodpasture,<sup>2</sup> Winternitz,<sup>3</sup> Klotz,<sup>4</sup> MacCallum<sup>5</sup> and Opie and associates.<sup>6</sup> Excellent material, however, was obtained at Camp Devens during the epidemic, and although Wolbach<sup>7</sup> has published a preliminary report on the pathology and bacteriology of these cases, the more complete study of this material has only just been made. As this study has brought out some interesting points which have not been emphasized by other workers, and as it is possible from this material to form a definite opinion in regard to the course of the lesions in the different organs and their relation to various bacteria present, it seems advisable to publish the results.

We appreciate that a decided difference of opinion exists in regard to the cause of this pandemic. The discussion has practically narrowed down to the question of whether the influenza bacillus or some unknown virus was the etiologic agent. Excellent points have been made both

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\* From the pathological laboratory and the medical clinic of the Peter Bent Brigham Hospital.

1 Goodpasture, I. W., and Burnett, F. L. The Pathology of Pneumonia Accompanying Influenza, U. S. Nav. M. Bull. **13** 177 (April) 1919.

2 Goodpasture, E. W. The Significance of Certain Pulmonary Lesions in Relation to the Etiology of Influenza, Am. J. M. Sc. **158** 863 (Dec.) 1919.

3 Winternitz, M. C., Wilson, I. M., and McNamara, F. P. The Pathology of Influenza, Yale Univ. Press, 1922.

4 Klotz, O. Studies on Epidemic Influenza. Univ. Pittsburgh School of Medicine Publications, 1919.

5 MacCallum, W. G. Pathological Anatomy of Pneumonia Associated with Influenza, Johns Hopkins Hosp. Rep. **20** 149, 1921.

6 Opie, F. L., Freeman, A. W., Blake, F. G., Small, J. C., and Rivers, T. M. Pneumonia Following Influenza, J. A. M. A. **72** 556 (Feb. 22) 1919.

7 Wolbach, S. B. Comments on the Pathology and Bacteriology of Fatal Influenza Cases as Observed at Camp Devens, Mass., Johns Hopkins Hosp. Bull. **30** 104 (April) 1919.

of the body This air, during life, first appeared in the subcutaneous tissue of the neck, having passed from the root of the lungs through the loose tissue of the mediastinum From the neck it extended in some cases over the entire trunk, head and extremities From a study of the lungs at necropsy and gross sections of them fixed in Kaiserling's fluid, it is felt that the acute interstitial emphysema results from the mechanical rupture of some of the pulmonary alveoli which have become distended by the acute alveolar emphysema which is characteristic of this disease The air then extends along the interlobular septums and reaches the hilus of the lung through the connective tissue accompanying the blood vessels Apparently, the connective tissue surrounding the bronchi is more compact and does not furnish a route for the air From the hilus of the lung the air travels subpleurally over the pericardium and great vessels into the loose tissue of the mediastinum In this series of twenty-six cases, the subcutaneous emphysema was present in five and emphysema of the mediastinum was found in five more In these ten cases in which the air had escaped from the alveolar spaces, the influenza bacillus was recovered by culture or demonstrated in sections of the lungs in nine Although other organisms than the influenza bacillus were present in the lungs in some of these cases, they were not present with sufficient regularity to make the lesions they produced responsible for the escape of the air From the number of cases in which it was present, the influenza bacillus may well be considered a causative factor in the occurrence of this escape of air, and even if it is only a complicating organism in the epidemic disease, it may be a necessary factor in producing this peculiar lesion As will be seen later, the pulmonary lesion of alveolar emphysema which leads to the escape of air occurs without the presence of the influenza bacillus, but the alveolar emphysema may not go on to actual rupture of the alveoli and interstitial emphysema formation without the presence of some complicating organism

The peritoneal cavity was normal in appearance in all twenty-six cases, although in one the appendix was acutely inflamed, so it can be said that the causative factor of the epidemic is not likely to produce a peritonitis

In this group of twenty-six cases, empyema was present in five, in two of which it was bilateral No cultures were taken from the pleural cavities in these five cases The cultures from the lungs and heart's blood and a study of the lung tissues showed both pneumococci and influenza bacilli present, and in one case other bacteria In five cases, one or both pleural cavities contained a moderate effusion of thin turbid yellow fluid, with evidence of inflammation on the pleural surfaces Had these patients lived longer, a frank empyema might have developed In these cases also no cultures were taken from the pleural cavities In



of the influenza bacillus and the absence of bacteria at the site of the uncomplicated pulmonary lesion suggest that some undiscovered virus produces these lesions in the lungs and presumably therefore is the cause of the epidemic.

The bacterium cultivated by Oltzky and Gates<sup>10</sup> from cases of this epidemic disease and called *Bacillus pneumovintes* has been recently advanced as the unknown virus which produces this disease. Its demonstration in sections of lungs of influenza has not yet been achieved.

For those who feel that the influenza bacillus causes the epidemic, these characteristic pulmonary lesions which were found without the presence of the influenza bacillus make it necessary to attribute to this organism the power to produce this injury to the lung before the bacilli themselves reach the alveoli. This might be accomplished by the mechanical action on the alveoli of a peculiar exudate in the bronchi and alveolar ducts due to the influenza bacillus or through toxins from these bacilli affecting the lungs. However, as mentioned above, in certain of these cases the influenza bacilli were neither found in the tissues nor recovered in culture.

#### CASE REPORT

In this series twenty-seven cases were studied. One of the patients died of a streptococcal septicaemia two days after the onset of the illness. The clinical course in this case was quite different from that of other epidemic cases, and the lungs at necropsy were free from anything suggesting pneumonia of any type. Streptococci were found in the blood vessels throughout the body. For these reasons this case has been omitted from the discussion, as it is thought that the patient did not have the epidemic disease.

#### SECONDARY FINDINGS

On gross inspection, certain lesions were found in various parts of the body in this group of cases, some of which, especially those in the lungs, were quite characteristic of this epidemic disease. As our endeavor has been to discover the sequence of events in the lesions of the various organs rather than to group and classify the various pathologic findings, the gross appearances will be presented with the description of the lesions in the different organs as they were worked out by microscopic study. Before taking up the description of the various organs, attention will be called to the lesions found at necropsy which were not studied with the aid of the microscope. Of these the most spectacular was the presence of air in the subcutaneous tissues

10. Oltzky, P. K. and Gates, F. L. Experimental Studies of the Nasopharyngeal Secretions from Influenza Patients, J. Exper. Med. 23: 713 (Feb.) 1921.

two of these five cases no influenza bacilli were recovered by culture or seen in the sections of the lungs. The bacteria present in the heart's blood and lungs were the influenza bacillus, streptococcus or another unidentified diplococcus, but they were not consistently present in all cases. From a survey of these cases of empyema and incipient empyema, there is insufficient evidence to permit the designation of any one organism as the cause of the empyema, and as there were always organisms present in the lungs, the pleural condition can hardly be considered due to some unknown virus. That empyema, pronounced or incipient, occurs frequently in these cases (ten out of twenty-six) is a fact, and it presumably is due to several of the complicating organisms.

An acute inflammation of the pericardium was found in only two of the twenty-six cases, and in both instances the pneumococcus was recovered in pure culture, so that it seems fair to rule out the cause of the epidemic as likely to produce a pericarditis.

Involvement of the middle ears or of some of the accessory sinuses to the upper respiratory tract occurred in all the nineteen cases in this series in which the head was opened at necropsy. Of the sinuses, the sphenoidal were involved more often than the others. In three of these nineteen cases, no bacteriologic examination was made on account of the length of time postmortem before necropsy was performed. In the remaining sixteen cases, a variety of bacteria were recovered, but the influenza bacillus predominated being recovered in fifteen of the sixteen cases. The influenza bacillus alone of these bacteria may reasonably be regarded as the causative agent of these infections in the ears and sinuses, if a conclusion is demanded, but, of course, it is well known that various organisms produce empyema of these cavities. The invasion by these organisms, which were recovered by culture, may also have been a secondary one after the tissue had been rendered more vulnerable by some unknown virus. Meningitis was found in only one of the nineteen cases in which the head was opened. In one other, an abscess of the brain was found, and in still another, an encephalitis was suspected. On account of the infrequency of cerebral lesions and as the meningitis was due to the pneumococcus, it seems fair to say that the cause of this epidemic, whatever it may be, is not likely to produce gross cerebral or meningeal lesions.

#### MICROSCOPIC EXAMINATION

Turning now to the various organs and tissues of the body which were studied microscopically<sup>11</sup> as well as by gross inspection, many interesting and instructive lesions were encountered. One of the first

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<sup>11</sup> In this study, the sections for microscopic examination were stained with eosin and methylene blue after Zenker's fixation. A few other special stains were also used.

of the body This air, during life, first appeared in the subcutaneous tissue of the neck, having passed from the root of the lungs through the loose tissue of the mediastinum From the neck it extended in some cases over the entire trunk, head and extremities From a study of the lungs at necropsy and gross sections of them fixed in Kaiserling's fluid, it is felt that the acute interstitial emphysema results from the mechanical rupture of some of the pulmonary alveoli which have become distended by the acute alveolar emphysema which is characteristic of this disease The air then extends along the interlobular septums and reaches the hilus of the lung through the connective tissue accompanying the blood vessels Apparently, the connective tissue surrounding the bronchi is more compact and does not furnish a route for the air From the hilus of the lung the air travels subpleurally over the pericardium and great vessels into the loose tissue of the mediastinum In this series of twenty-six cases, the subcutaneous emphysema was present in five and emphysema of the mediastinum was found in five more In these ten cases in which the air had escaped from the alveolar spaces, the influenza bacillus was recovered by culture or demonstrated in sections of the lungs in nine Although other organisms than the influenza bacillus were present in the lungs in some of these cases, they were not present with sufficient regularity to make the lesions they produced responsible for the escape of the air From the number of cases in which it was present, the influenza bacillus may well be considered a causative factor in the occurrence of this escape of air, and even if it is only a complicating organism in the epidemic disease, it may be a necessary factor in producing this peculiar lesion As will be seen later, the pulmonary lesion of alveolar emphysema which leads to the escape of air occurs without the presence of the influenza bacillus, but the alveolar emphysema may not go on to actual rupture of the alveoli and interstitial emphysema formation without the presence of some complicating organism

The peritoneal cavity was normal in appearance in all twenty-six cases, although in one the appendix was acutely inflamed, so it can be said that the causative factor of the epidemic is not likely to produce a peritonitis

In this group of twenty-six cases, empyema was present in five, in two of which it was bilateral No cultures were taken from the pleural cavities in these five cases The cultures from the lungs and heart's blood and a study of the lung tissues showed both pneumococci and influenza bacilli present, and in one case other bacteria In five cases, one or both pleural cavities contained a moderate effusion of thin turbid yellow fluid, with evidence of inflammation on the pleural surfaces Had these patients lived longer, a frank empyema might have developed In these cases also no cultures were taken from the pleural cavities In

Associated with these injuries to the muscle fibers were congestion and actual hemorrhage into the supporting connective tissue of the muscle. As no lesion was detected in the larger blood vessels, it was presumed that the hemorrhage came from the capillaries. If the patient survived a cellular reaction appeared, consisting chiefly of polymorphonuclear neutrophils and mononuclear phagocytes. These cells invaded the necrotic muscle, surrounded the partially injured fibers and grouped themselves in the interstitial tissue. The polymorphonuclear cells in this exudate became much fewer before many days, and the blood cells from the hemorrhage also soon disappeared. The necrotic muscle was removed by the action of the invading phagocytic cells and probably in part by some enzymatic action without cellular reaction.

Repair of the injured muscle fibers in which the sarcolemma remained was carried on from the sarcolemma from which new fibrils were formed, and eventually a new fiber appeared. In those instances in which a part of the old fiber remained, the new became continuous with it. These new fibers could usually be detected by the fact that with the eosin and methylene blue stain they took the eosin stain less intensely. Also the number of nuclei in the sarcolemma was increased. Gradually the cellular reaction disappeared and the repaired muscle returned toward its normal appearance, with practically no permanent increase in the supporting connective tissue.

The muscle lesion in these cases was the one that has been described before, and is known as Zenker's degeneration. Usually it does not occur in uncomplicated lobar pneumonia and therefore its appearance may be of assistance in detecting a pneumonia secondary to this disease in the absence of an epidemic. This muscle lesion, however, has also been noted by MacCallum<sup>13</sup> in streptococcus pneumonia following measles in army camps.

The heart muscle itself seemed to escape demonstrable injury in this epidemic disease. In two instances, the endocardium showed an acute lesion on one of the valves which consisted of a vegetation in which some organization was taking place. The infrequency of this lesion on the endocardium, and the fact that in one instance a pneumococcus was recovered from the heart's blood, makes it seem unlikely that the cause of the epidemic, whether the influenza bacillus or some unknown virus, was responsible for the lesions. In one case, a small area of cellular infiltration, consisting chiefly of mononuclear cells but with a few polymorphonuclear leukocytes and mast cells, was seen in the tissue about a blood vessel in the myocardium, but this isolated observation was not considered to be of any practical importance.

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13 MacCallum, W. G. Monograph No. 10, Rockefeller Institute for Medical Research, 1919.

to appear on opening the body was a lesion in the rectus muscle of the abdominal wall. Such a lesion on gross inspection was reported in nine of the twenty-six cases. In fourteen the muscle was reported as normal in appearance, and in three no observation was made on the condition of the muscle. In none of these nine cases in which a lesion of the rectus muscle was noted was a culture made from it. On study under the microscope, however, no organisms were found in eight of the nine cases. In the ninth, a coccus was found in the leukocytes at the site of the lesion. The absence of organisms in the vast majority of the cases makes it seem quite certain that this injury to the muscle was the result of some circulating toxin rather than any organism. In the cases in which the lesion occurred, a variety of organisms were encountered in cultures or sections from the lungs. Of these organisms, the influenza bacillus was most consistently present. If this lesion is a toxic one, it may be the result of some toxin from the influenza bacillus or the unknown virus of the epidemic. No other organism was present in the lungs sufficiently often to be looked on as a specific cause. This lesion in the muscle is similar to the one which has been noted in various acute infections, such as, for example, typhoid fever. As abscesses have been reported in muscles in cases of this epidemic in which the patient survived for some time, it is thought that the appearance of a coccus in the lesion in one of these cases was a secondary invasion, and that this is the explanation of the abscess formation noted clinically in cases of this epidemic by one of us<sup>12</sup>

The injured muscle in these cases showed, in the gross, a swelling of the muscle fibers with increased friability. In most of the cases, actual hemorrhage had occurred into the muscle substance, separating the muscle bundles and in a few instances extending beyond the muscle into the adjacent subperitoneal tissues of the abdomen and pelvis. On microscopic study, it was worked out that the initial step in this lesion, which in some fibers went on to complete necrosis, was a swelling of the muscle fibers with loss of the striations and loss of nuclei. In other instances, the central part of the fibers apparently became necrotic, but the sarcolemma survived, and evidences of regeneration were shown by an increase of the nuclei. In some fibers, a part showed these degenerative changes, and the remaining part appeared normal. In other fibers, slight changes in the staining reaction of the fibers occurred, but no difference in appearance of the nuclei was observed except that they were more numerous than normal. This was looked on as the slightest perceptible injury to the fiber. The extent of the injury to the individual fibers and the number of fibers involved varied in different cases.

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12 Frothingham, C. Contributions to Medical and Biological Research, Dedicated to Sir William Osler 1 513 1919

mixed one with a variety of organisms and the microscopic examination of the spleen presented nothing unusual in addition to the abscess. Fibrin at the center of the lymph follicles without pronounced reaction about it except an increase in the polymorphonuclear leukocytes was not infrequently encountered. In a few instances, the red blood cells seemed to have broken out of their capillaries, and in a few others the number of polymorphonuclear leukocytes seemed increased throughout

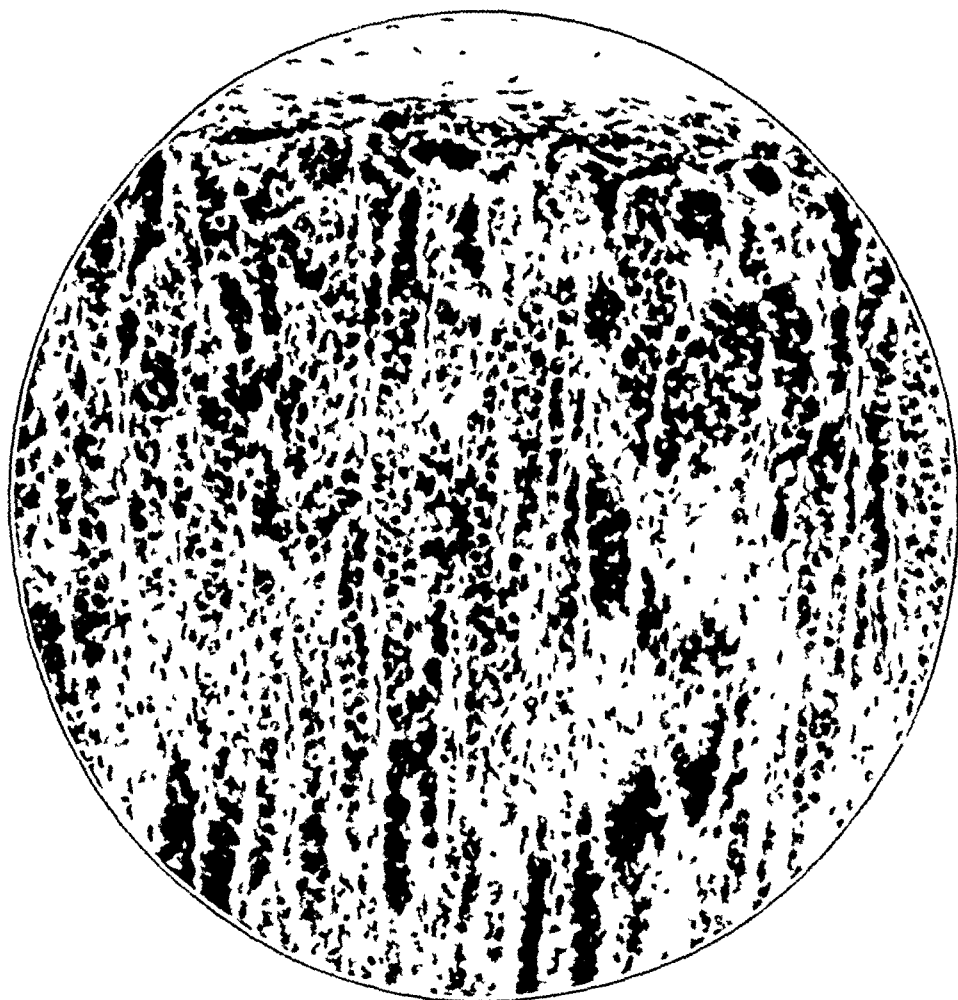


Fig 1—Cortex of suprarenal showing loss of cortical cells in fascicular zone. The disappearance of cells is preceded by disappearance of lipoid material. Low power photomicrograph.

the spleen. The hyaline change in the walls of the small arteries which is so common in the spleen, especially in those dying of acute infection, was frequently seen.

On gross examination the suprarenals were reported normal except in one instance, in which there was a hemorrhage into the substance of the gland, so that no gross lesion can well be ascribed to the cause of the epidemic. On microscopic study, however, a lesion of the cortical cells was observed in sixteen of the twenty-four cases studied. In two

On gross inspection, the livers in these cases presented no lesions of importance that could be attributed to the causative agent of the epidemic. In one instance, acute congestion was suspected and in another focal necrosis. On microscopic study, several slight lesions were found in some cases. Of these, the most frequently encountered was an infiltration of cells in the connective tissue about the smaller bile ducts. These cells were in most cases entirely mononuclear, but in a few instances polymorphonuclear leukocytes were also present. This cellular reaction was observed in twelve of the twenty-six cases. As it occurred in less than half of the cases, and as this lesion is often encountered in necropsy material from other sources, and as in these cases various bacteria were present, the most that can be said in regard to the cause of the epidemic in relation to this lesion is that it may be one of the various agents responsible for it.

In three of the cases, the parenchymal cells in the midzonal region showed slight changes in their staining reaction in that their cytoplasm stained more purplish with the eosin and methylene blue stain than the other cells, and their nuclei stained a deeper blue and appeared more homogeneous. In this part of the lobule, the red blood cells seemed more numerous in the sinusoids, but there was no cellular reaction or actual necrosis of the parenchymal cells. As this slight lesion occurred in only three cases, it was felt that it had no important relation to the cause of the epidemic. In seven cases, degenerative changes about the central veins (hepatic) of the lobules was seen. This lesion varied from slight vacuolization in the liver cells with slight variation in the staining reaction to actual necrosis of the cells with invasion of the necrotic cells by phagocytes and an increase of leukocytes in the surrounding sinusoids. No organisms were found about these lesions. As this lesion of central necrosis in the liver is quite commonly associated with other infections, and as various bacteria were found in these cases, it is not possible from these few cases to attribute this lesion in this group to any one cause. It may be said that the cause of this epidemic may be another agent which produces central necrosis in the liver.

In this series of cases, the spleens did not present any peculiar lesion nor one that occurred with sufficient frequency to make it apparent that the cause of the epidemic was necessarily responsible. Such lesions as were seen in the gross and microscopically are frequently encountered in the infections with the various types of organisms found in the lungs in these cases. The cause of the epidemic, however, may be another agent which produces these lesions. In the gross one case of congestion, five cases of acute splenitis, one case of infarction, and one case of abscess were described. On microscopic study, a tubercle was found in one of the five cases described as acute splenitis. In the case with abscess of the spleen the infection in the lungs was a

in a patient who survived for nearly five weeks, the capillary walls of the tufts were somewhat thickened, which was looked on as possibly the end result of this acute lesion.

No bacteria were found in any of these lesions, and it was felt that it was a toxic one. Such a lesion occurs in a variety of acute infections produced by the organisms present in these six cases, so that the cause of the epidemic, whether the influenza bacillus or some other virus, could only be looked on as possibly another agent capable of producing this acute glomerular lesion.

In the pancreases in this series of cases, no abnormalities were described in the gross, and on microscopic examination no lesions of importance were found, so that it may be said that the cause of the epidemic does not produce a demonstrable lesion in the pancreas.

On gross inspection the gastro-intestinal tract showed a variety of slight lesions but not one with sufficient frequency to make it seem likely that it bore any special relation to the causative agent of the epidemic, especially as the lesions seen are known to occur in various acute infections produced by the bacteria present in these cases. In one instance acute appendicitis was present. In one case injected areas were seen in the cecum and ileum; in another congestion of the gastric mucosa, and in two others actual hemorrhagic spots in the stomach wall. In one instance, actual hemorrhage had occurred into the lumen of the stomach, and in one case with emphysema of the mediastinum, an air bubble was found in the wall of the stomach toward the cardiac end. On microscopic study of the gastro-intestinal tract, which was carried out on only ten cases, no distinctive lesions were found. In several instances, lesions such as are found in acute infectious diseases were seen, such as thrombosis in small vessels, punctate hemorrhages, small areas of cellular reaction and migration of polymorphonuclear leukocytes toward the lumen of the intestine, but on account of the infrequency of these lesions and their occurrence in other infections they apparently were of no importance in relation to the cause of the epidemic.

The testicles in these cases presented, on microscopic study, an interesting lesion which occurred with sufficient frequency to make it seem associated with the cause of the epidemic or the most frequent complicating organism, namely, the influenza bacillus, especially so as the lesion is not ordinarily encountered in acute infections produced by the other complicating organisms found in these cases. The early stages of this testicular lesion, however, have been described adequately by Mills<sup>14</sup> in cases of pneumonia following measles as well as in cases

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<sup>14</sup> Mills, R. G. The Pathological Changes in the Testes in Epidemic Influenza, *J. Exper. M.* **30** 505 (July) 1919.



instances, sections from the suprarenal glands were missing. This lesion varied from a simple degeneration of the epithelial cells of the cortex shown by the appearance of vacuoles in the cells and a difference in the staining reaction to actual necrosis of the cells with invasion by phagocytes and a cellular reaction of leukocytes in the surrounding tissues. In the milder cases, repair takes place by the formation of new cells from the adjacent parenchyma, as evidenced by mitoses, but in the more pronounced cases, mononuclear cells invade, and groups of these cells remain in areas from which the gland cells have disappeared and in which there may be some slight increase of connective tissue. This type of lesion in the cortex of the suprarenal is frequently encountered in a variety of acute infections. Its presence in such a large number of these cases makes it seem probable that either the influenza bacillus, which was present so frequently, or some other virus responsible for the epidemic may be another of the causes which produce this lesion in the suprarenal cortex. As no organisms were found in these lesions, it is presumed that they were produced by toxins rather than by the actual presence of an organism.

In the medullary part of the suprarenal gland, in eight instances, there were found small groups of round cells, chiefly of the lymphoid and plasma types. These groups of cells occurred without apparent destruction of the medullary cells or other reason for their appearance. These cell groups in the medullary portion of the suprarenal occur in various conditions, and as they only were found in a third of these cases, it is felt that the lesion bears little relation of importance to the cause of the epidemic, which, however, may possibly be another of the factors responsible for their production.

The kidneys presented no lesions of importance on gross inspection in this series. In eight of the twenty-four cases studied (in two instances no sections of the kidneys were preserved) a microscopic lesion was seen. Of these eight cases, two showed simply areas of cellular infiltration consisting of lymphoid cells and polymorphonuclear leukocytes scattered at irregular intervals throughout the kidney substance. The cause of these groups of cells was not apparent, nor was it evident that any damage of importance had occurred in the renal tissue. In the other six cases, a definite glomerular lesion was present which consisted of a proliferation of the endothelial cells lining the glomerular capillaries and an increase in the number of polymorphonuclear leukocytes in the glomerular tufts. In some instances, there was also an increase in lymphoid cells and polymorphonuclear leukocytes about the capsule and among the tubules, which suggested that the toxic lesion had in some instances injured the epithelium of some of the tubules and called forth slight cellular reaction. In one instance,

were found in the sections, so it is presumed that the lesion was a toxic one. The primary disturbance was a degeneration of the epithelial cells of the tubules as evidenced by loss of the cell outline, especially in the deeper layers and pyknosis of the nuclei. Evidence of mitosis disappeared and the epithelium separated as a whole from the underlying basement membrane. In some instances, edema in the interstitial tissue was present. If mild, this lesion was unassociated with cellular reaction, but if extensive and severe, a moderate cellular reaction of lymphoid cells, polymorphonuclear leukocytes and mast cells occurred in the connective tissue framework for the tubules. The interstitial cells of the testicle seemed to be unaffected by this process.

Soon after the degeneration and desquamation of the epithelial cells, a deposit of hyalin collagen with nuclei in it appeared on the gland side of the basement membrane and extended out into the mass of injured epithelial cells in places. In the more severe cases this material was so extensive that it left the tubules in the later stages entirely sclerosed as this hyaline material eventually seemed to change into definite connective tissue. In the milder cases the sclerosis of the tubules was only partial. The basement membrane of the tubules became thickened as the process healed. No evidence of regeneration of the epithelium of the tubules was made out and it is a question as to how well these tubules would have functioned again had the patients lived. In some instances after healing there seemed to be an increase in the interstitial connective tissue.

The aortae in these cases were reported as normal on gross inspection in eight of the twenty-six cases. In one instance, lesions suggesting syphilitic aortitis were found, and in the remaining seventeen cases mild involvement of the intima with typical early arteriosclerotic changes occurred. On microscopic study of the aortae the intimal lesion was usually the one found in a variety of conditions consisting in a cellular invasion chiefly of mononuclear cells, often laden with fat, and occasionally a polymorphonuclear leukocyte, together with a slight fibrous thickening of the intima. There was nothing peculiar to the lesion in these cases, and if it was due to the cause of the epidemic, it simply means that this is another one of the many agents which produce this arterial change.

#### EXAMINATION OF THE LUNGS

The lungs in each case in this series presented both gross and microscopic lesions. Considerable confusion has been created in regard to the gross and microscopic lesions due to this epidemic disease, because the pathologists who have reported on the pulmonary lesions have not always endeavored to separate the lesions due to the virus

of influenzal pneumonia. In the cases in which this lesion occurred, the influenza bacillus was always present, so that no decision can be reached as to whether the influenza bacillus or the virus of the epidemic, if they are separate, is the cause of this injury to the testicle.

Gross inspection of the testicle and the threading of the tubules failed to disclose this lesion, because in only one of the twelve cases in which the lesion occurred was anything abnormal reported in the

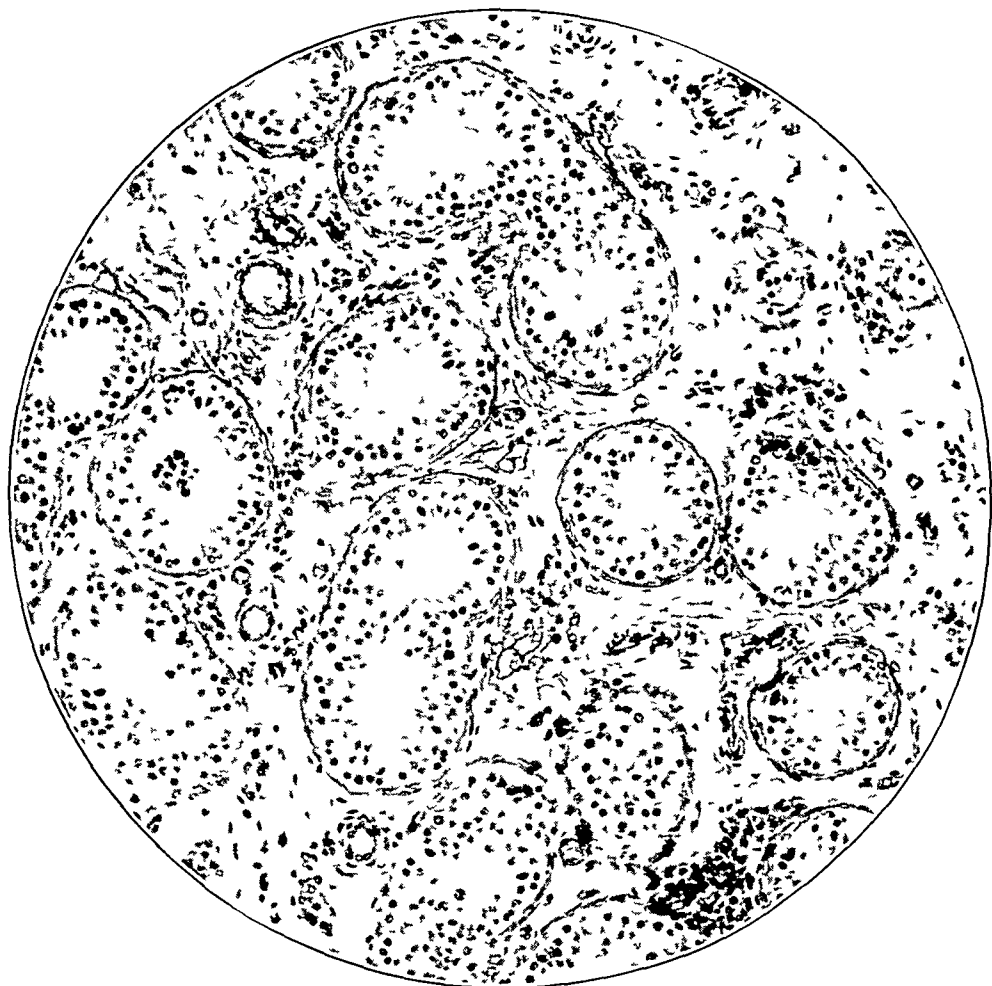


Fig 2—Testicle showing aspermia, thickening of basement membrane and edema of the interstitial tissue. Low power photomicrograph.

gross, and, furthermore, in one other in which interstitial orchitis was reported from the gross study, the testicle appeared normal under the microscope.

Unfortunately microscopic study of the testicles was only carried out in seventeen of the cases, but in twelve of these the special lesion was found in them in some degree. It was possible to follow the lesion from its start to the end result in these twelve cases. No organisms

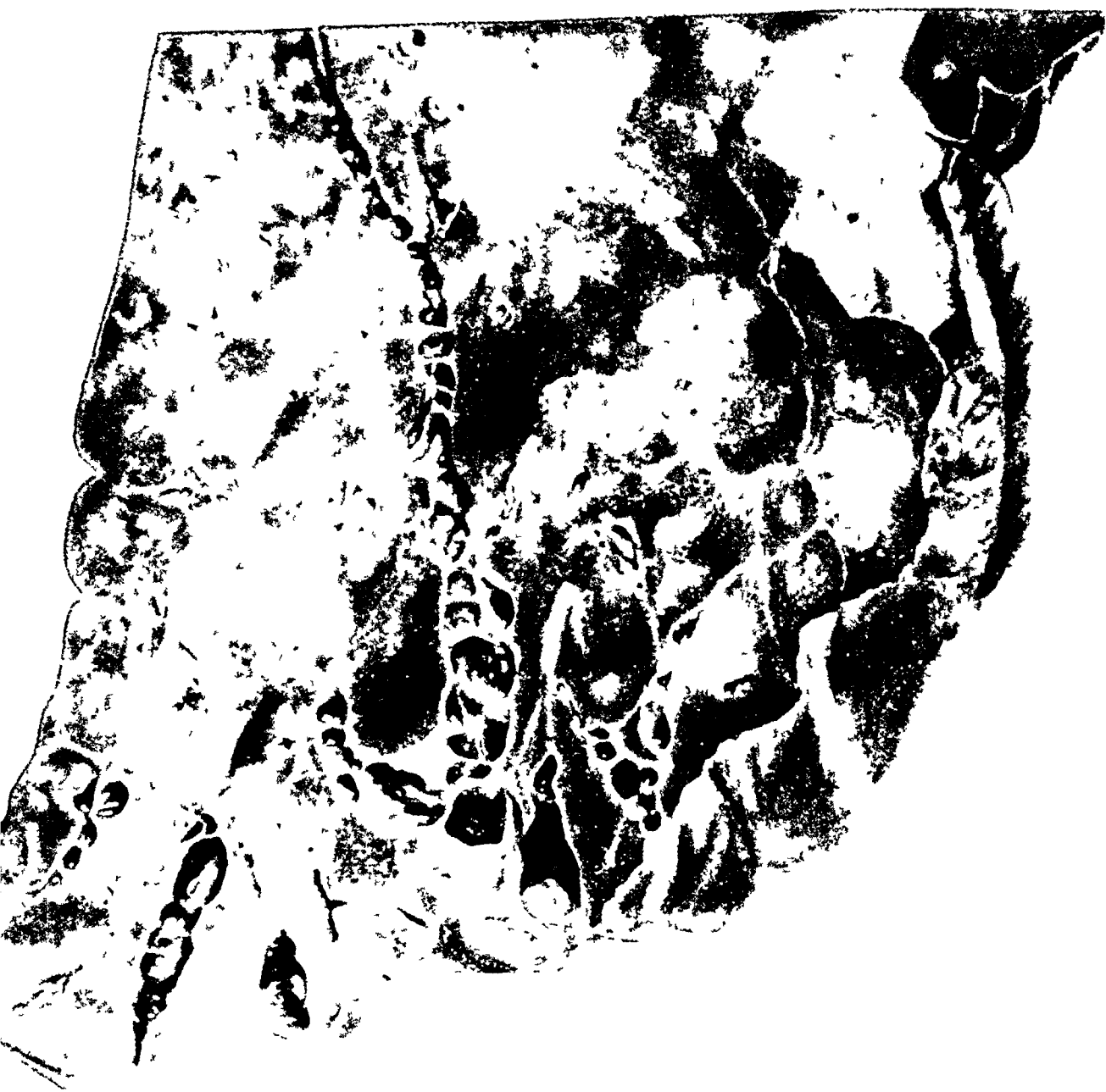


Fig 4—Appearance of virus lesions in lung followed by influenzal bronchitis, peribronchitis and bronchopneumonia. There is marked alveolar emphysema and interstitial emphysema, and the dissection of air toward the hilus of the lung is shown.

of the epidemic and those dependent on the complicating organisms. On account of the variety of complicating organisms, manifold gross pathologic appearances have been described, and a sharp separation between the lesions produced by the virus of the epidemic disease and the complicating organisms has not been made.



Fig 3—Cut surface of a hardened influenza lung, showing the pathologic condition of the uncomplicated virus lesion, namely, acute alveolar emphysema and hemorrhagic exudate. A portion of the pleura is included and shows the dusky red mottling which accompanies this lesion.

In forming an opinion in regard to the lesions produced by the virus of the epidemic, the study of these cases from Camp Devens has been supplemented by some material from the Peter Bent Brigham Hospital, and an analysis of the published studies on influenzal pneu-

monia mentioned above. All of the workers in this field have recognized lesions occurring early in the lung involvement which are not present in cases of lobar and bronchopneumonia unassociated with this epidemic disease. It is felt that it is now possible to pick out and arrange in sequence the lesions produced by the virus of the epidemic disease and



Fig 5—A tangential section through a hardened lung, showing alveolar emphysema, bronchitis and peribronchitis and marked thickening of interlobular septums. There are a few bronchiectatic cavities at both ends of the section.

follow the course of these lesions even in the presence of those produced by complicating organisms.

The lesions peculiar to the virus of the epidemic and their relation to the different bacteria and other pathologic processes will be described



to the presence of dilated air spaces. Also in some instances air vesicles were visible beneath the pleural surface and along the supporting tissue of the lungs. This picture was not uniformly distributed throughout the lungs but was limited in some cases to certain of the lobes.

This gross appearance of the lungs, which was considered to be due to the virus of the disease, was quickly complicated by the lesions of different bacteria, and in the gross more than microscopically in some instances the characteristic features of the virus lesions were obscured by the superimposed reactions.

Thus, even in the early stages, the hemolytic streptococcus infection would mask to a considerable degree the lesions due to the virus of

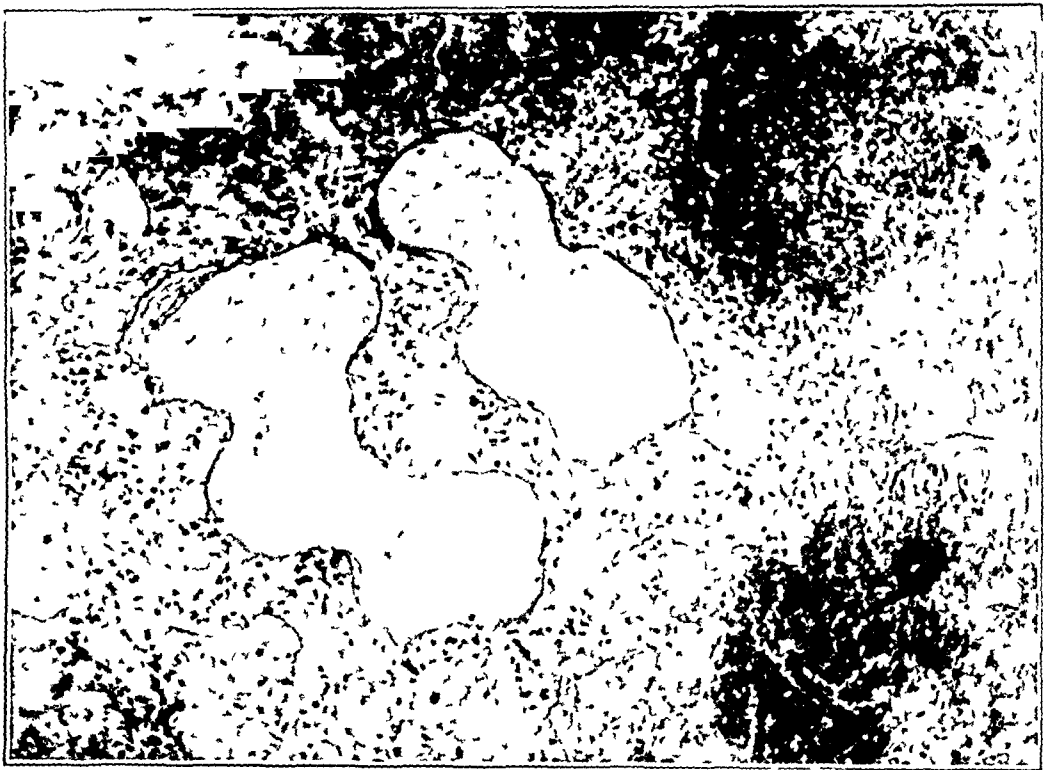


Fig 7—Low power photomicrograph illustrating the uncomplicated virus lesion of influenza in the lung, acute alveolar emphysema, hyaline membrane and hemorrhagic exudate

the epidemic disease. It is noteworthy that this streptococcus was a predominating secondary invader in some localities and that it invaded the lungs early. The pneumococcus infections presented the characteristic consolidations due to this organism, which were either lobular, lobar or patchy in distribution. The staphylococcus infections caused multiple abscesses. The influenza bacillus was frequently present in abundant numbers without masking the virus lesion. Also the influenza bacillus produced in these cases and maintained a definite type of bronchitis, bronchiectasis, and peribronchitis after the initial virus lesion had subsided. In these cases, the smaller bronchi were promi-



in detail later. In general, the lesion consists of an alveolar emphysema with an accompanying hemorrhagic exudate, in some instances interstitial emphysema, and the formation of a hyaline membrane in the alveoli and the alveolar ducts.

On gross inspection in the earliest fatal cases, partially collapsed lax lungs were seen which on section presented wet deep red surfaces



Fig 6—Two sections from an influenzal pneumonia case followed by pneumococcus lobular pneumonia. The effects of the virus lesion are shown by the alveolar emphysema and the interstitial emphysema. The arrows point to the bullae of interstitial emphysema. Slightly reduced.

yielding a blood tinged serous liquid from some areas and deep red liquid of the consistency of blood from others. On close inspection, especially when the cut surfaces were washed, the air-containing portions were found to be coarser in texture than the normal lung, owing

the influenza bacillus. In different lobes of the lung in one person a different gross appearance was at times encountered, because the secondary invading organisms varied.

In each of these cases from the Camp Devens series organisms were recovered by cultures or found on microscopic examination of sections of the lung. In some of the early cases in which organisms were only found in the sections, the distribution of them was in the bronchi and

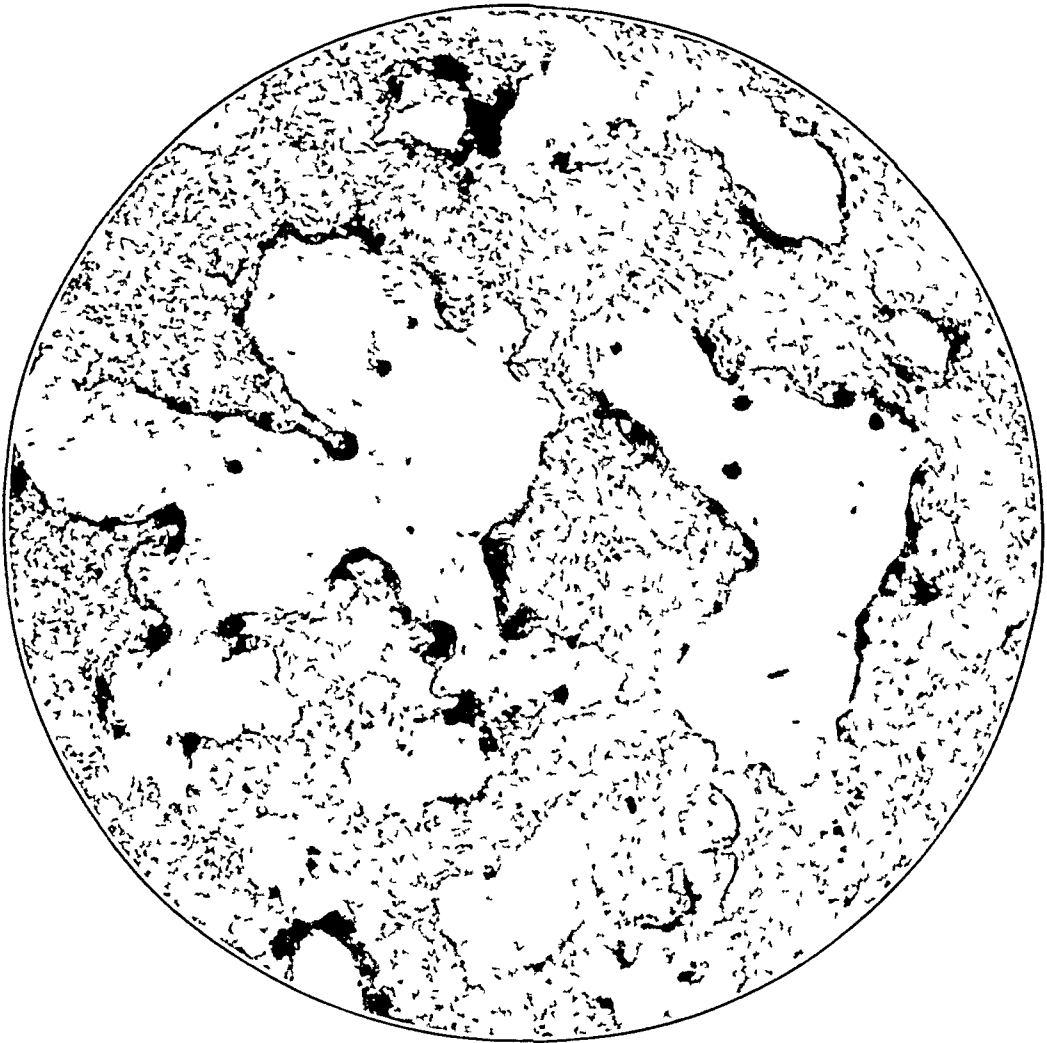


Fig 9—Low power photomicrograph of the virus lesion and an early bacillus influenzal bronchopneumonia, the former indicated by the acute alveolar emphysema and hyaline membrane, the latter by the infiltration with polymorphonuclear leukocytes.

not in the alveolar regions. Of the various organisms found, the influenza bacillus was seen much more frequently than other organisms, such as the pneumococcus and the streptococcus. It was found in twenty-two of the twenty-six cases. In a few of the cases in which death occurred after a relatively short time, from seven to ten days

nent on cut section, and their dilatation was apparent. These peribronchial lesions at times were so extensive that they coalesced and made the whole lung practically solidified.

These various types of consolidation and bronchial lesions became more pronounced and the typical virus lesion became less evident in cases in which the patient survived a week or more after the extension of the disease into the lungs. As MacCallum<sup>5</sup> has emphasized, it is

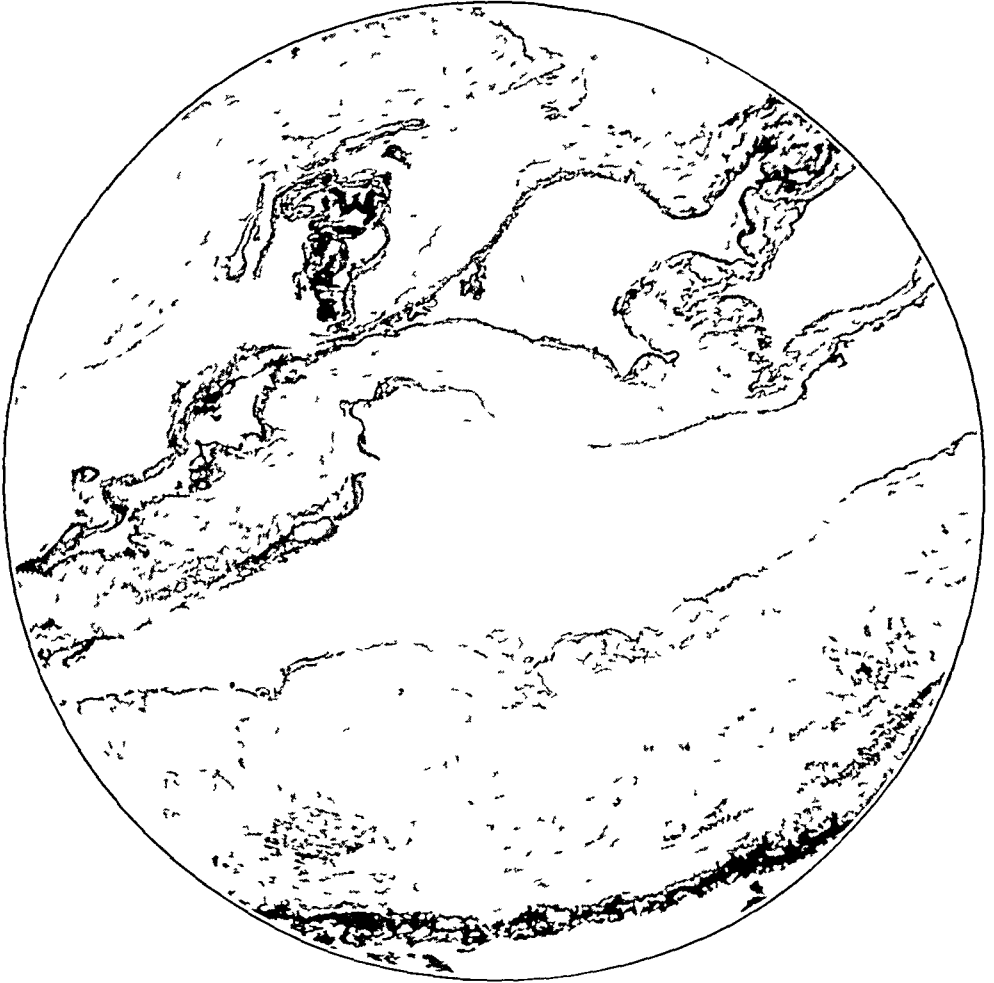


Fig 8—Section from the mediastinum. Interstitial emphysema in a case of pneumococcus mediastinitis. Note that the spaces occupied by air are lined with a hyaline membrane similar in appearance and staining reaction to the hyaline membrane found in the acute alveolar emphysema of the lungs in uncomplicated influenzal pneumonia. Low power photomicrograph, about 120 diameters.

possible to pick out in the gross the lesions due to the streptococcus, the staphylococcus as described by Chickering,<sup>15</sup> the pneumococcus and

15 Chickering, H. T., and Park, J. H. Staphylococcus Aureus Pneumonia, *J. A. M. A.* 72: 617 (March 1) 1919.

In a detailed description of the different processes in the lungs it is important to keep in mind the difference between the pulmonary lesion peculiar to the virus of the epidemic and the various lesions produced by the secondary invading organisms. For convenience, the lesion due to the virus of the epidemic disease will be called the virus lesion in the following description. In order to simplify the description, an outline of the development and repair of this virus lesion will be given.

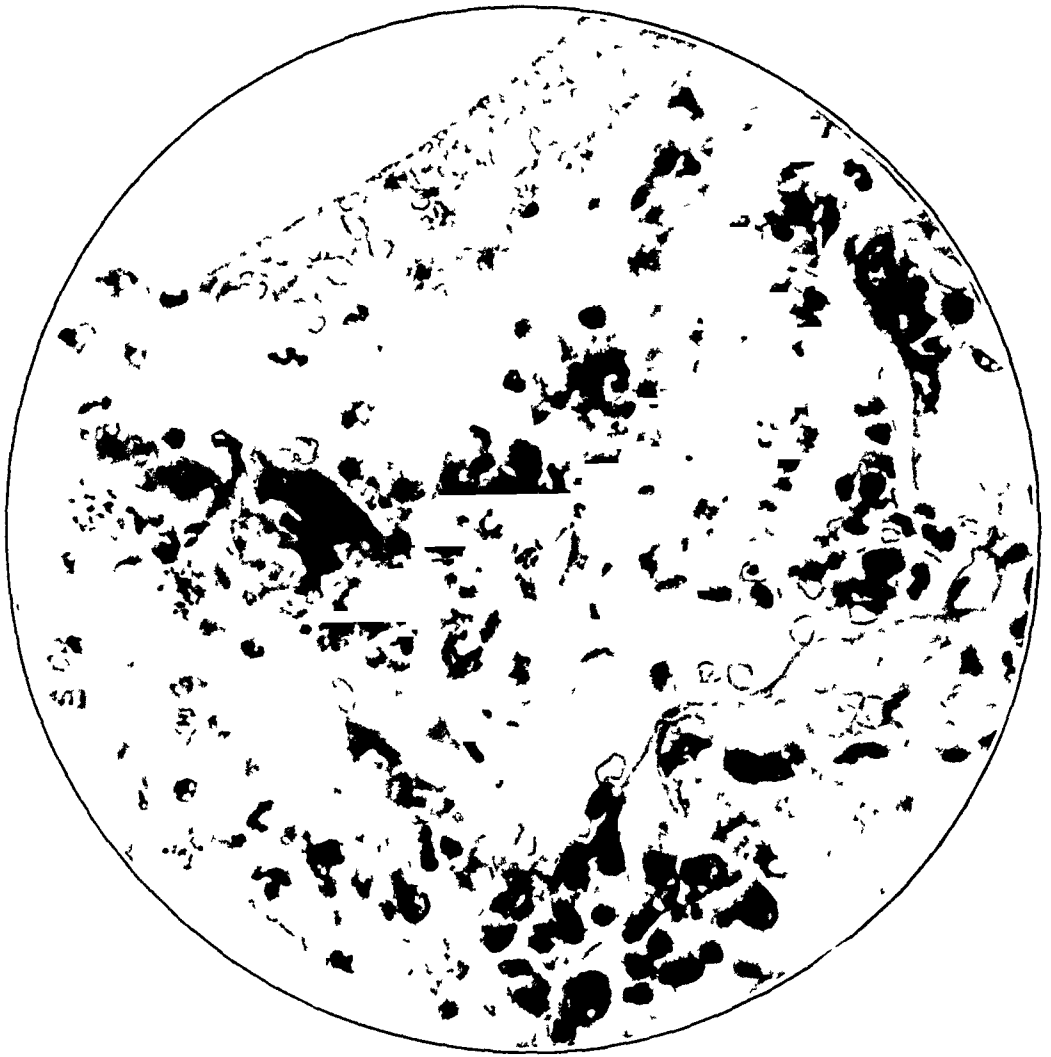


Fig. 11—Photomicrograph about 700 diameters illustrating the early repair of a hyaline membrane, namely, the invasion with polymorphonuclear leukocytes and macrophages.

as it was seen on microscopic study of the lungs. As secondary infection was present in each instance, it is not possible to decide whether certain of the existing pathologic processes would have occurred had the virus lesion remained uncomplicated. The earliest death in this series occurred seven days after the onset of the epidemic disease and the latest thirty-two days after the onset.

from the start of the epidemic disease, the influenza bacillus was not recovered by culture or seen in sections of the lung

In all but one of these cases (the exception being the patient who survived over four weeks) the peculiar pulmonary lesion mentioned above was present. It was felt, however, that this lesion was not produced by any of the bacteria present since this lesion was found in one early case in which the only bacterium present was an unidentified coccus found in the stained sections in the bronchial exudate. Also, in two other early cases in which the pneumococcus with the usual pneu-

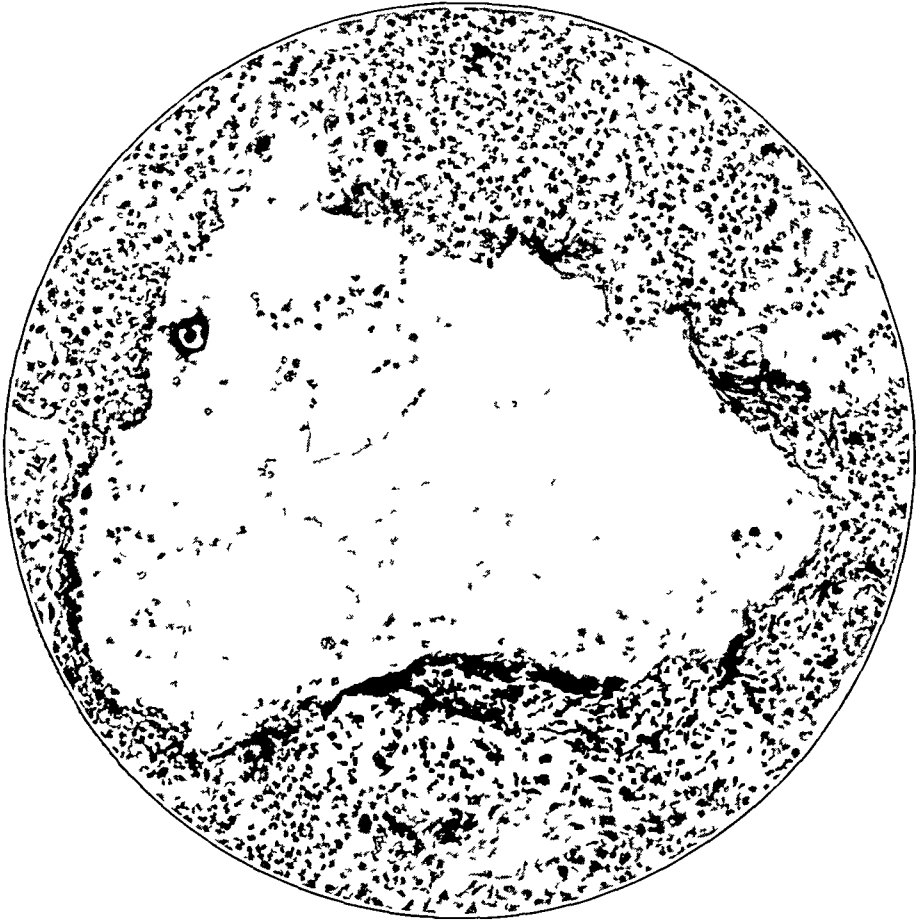


Fig 10—A higher power photomicrograph of field in Figure 9 to show the polymorphonuclear leukocyte exudate as a result of the *Bacillus influenzae* infection

mococcus lesions was the only organism present in the lungs, this peculiar lesion was present in its early stages. Thus, in three cases in which the influenza bacillus was not present this characteristic lesion was found, which is strong evidence against the influenza bacillus or its toxin being the cause of this lesion. No other organism was found in even a majority of the cases, so that it is not reasonable to consider these other bacteria encountered in this group as the cause of this pulmonary lesion.

sometimes appeared to have replaced the walls. In other places, desquamated epithelial cells or red blood cells and leukocytes lay between the hyaline membrane and duct or alveolar walls. In general, the arrangement and outline of this hyaline material suggested that its position was an effect of air forced into exudate. Of just what this hyaline membrane was composed was not determined, but apparently it was related to the action of the air and virus on some of the body fluid or exudates in this particular disease and not, as some claim, to the degenerated epithelium because in two cases in which the air had escaped from the lungs this same hyaline membrane was found in the

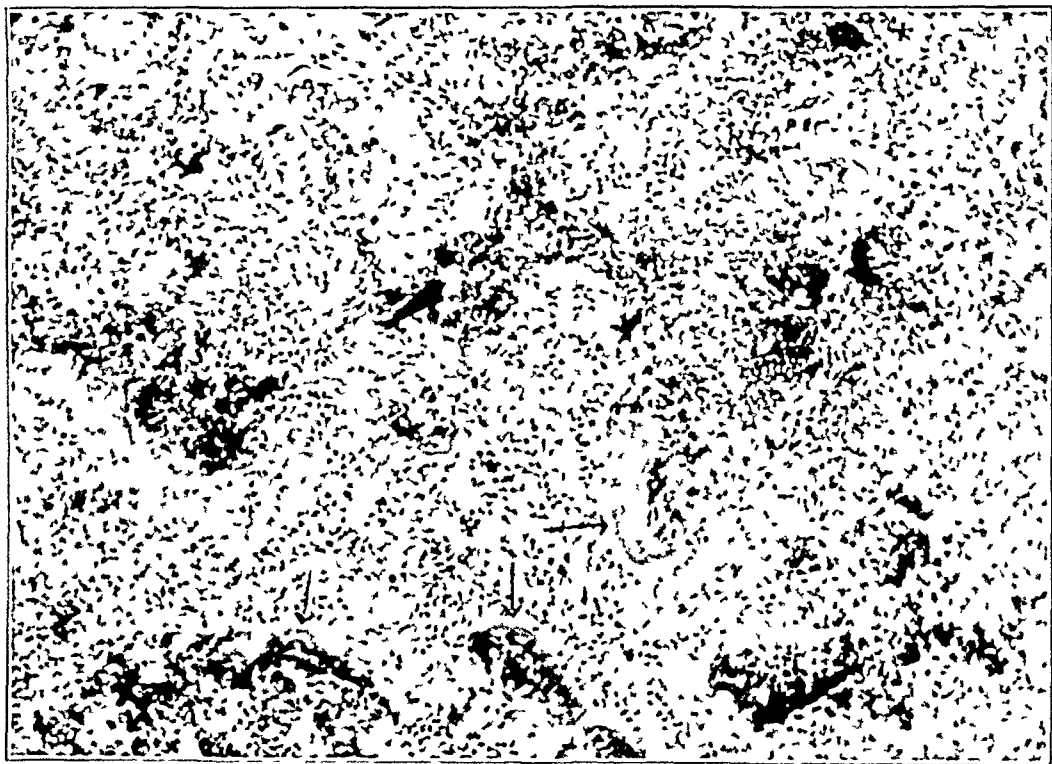


Fig 13—Low power photomicrograph of a lung with a virus lesion of influenza with a superimposed pneumococcus lobar pneumonia. The arrows point to hyaline membrane. The fibrinopurulent character of the exudate is shown. From our series of cases, the complete filling of emphysematous alveoli and alveolar ducts with exudate is brought about only by pneumococcus infection.

tissues of the mediastinum where no epithelium existed. In both of these cases, there was a pneumococcus pericarditis and an acute puriform infiltration of the fat and areolar tissue of the mediastinum. There was also a penetration of air bubbles into the mediastinal tissues and wherever the air came in contact with this exudate, the hyaline membrane was found. It is felt that for the formation of this membrane the air must be under some tension in its contact with the exudate.

The virus lesion at the start consisted in an injury to the epithelial cells of the smaller bronchi, the bronchioles, the alveolar ducts and the lining of the alveoli themselves, desquamation of this epithelium and disappearance of it. In some places considerable strips of desquamated epithelium were seen detached from the basement membrane but still preserving a normal staining reaction. At the same time, there was intense congestion of the blood vessels in these areas, and although no

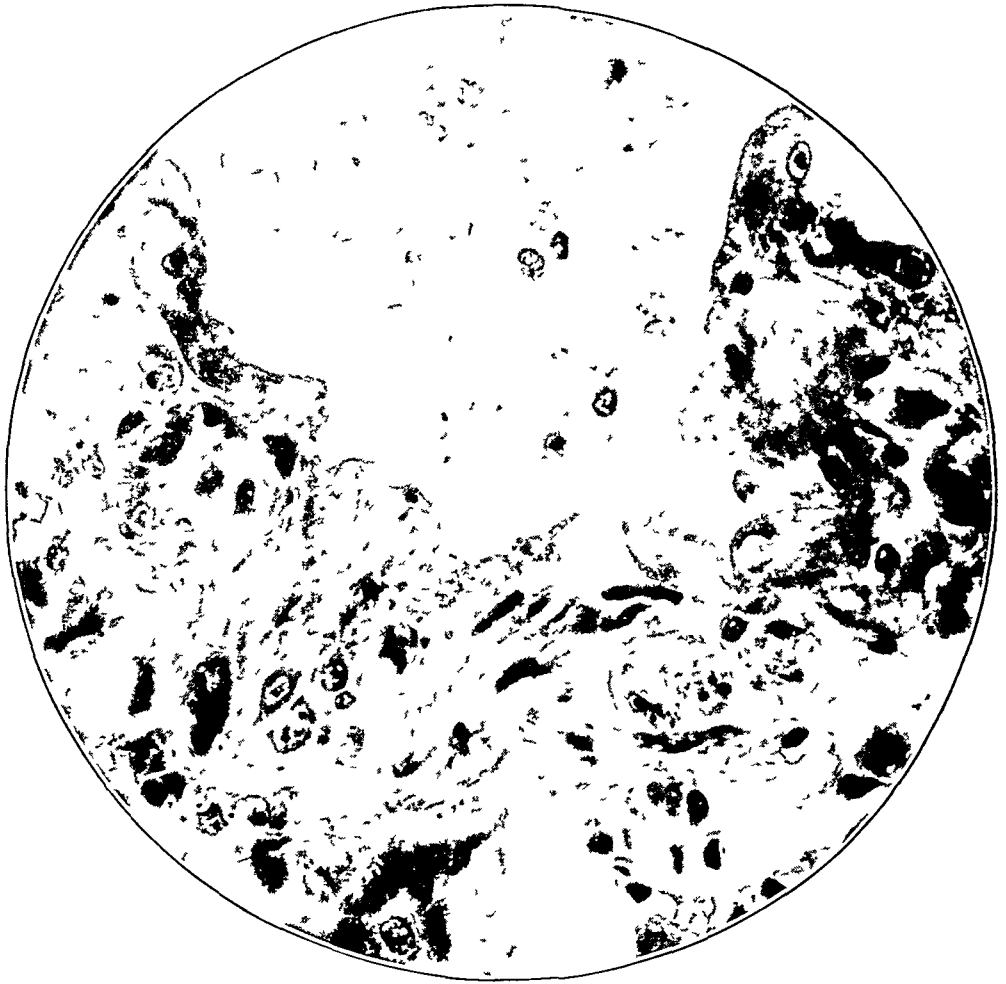


Fig 12—Photomicrograph of the virus lesion, about 700 diameters, showing a later stage in the repair of the virus lesion of the lung. The organization of the hyaline membrane is evidenced by the ingrowth of fibroblasts.

actual injury to the blood vessels could be made out, there must have been an injury because the red blood cells had broken out into the lumen of the bronchial tree and the alveolar spaces and a slight amount of fibrin had been deposited. In addition, a hyaline-like membrane was found in the alveolar spaces. This membrane outlined cell-free spaces presumably occupied in life by air. In places, the membrane was closely applied to the walls of the alveolar ducts and alveoli and

lungs The reaction associated with the secondary invading organism varied somewhat with the organism, and the different processes seen will be discussed below First, however, the process of repair of the virus lesion will be considered The hemorrhage was cleared up by the taking up of the red blood cells by endothelial phagocytes, as cells of this type filled with red blood cells were seen The epithelial lining of the bronchial tree and the alveolar spaces regenerates, as was evident

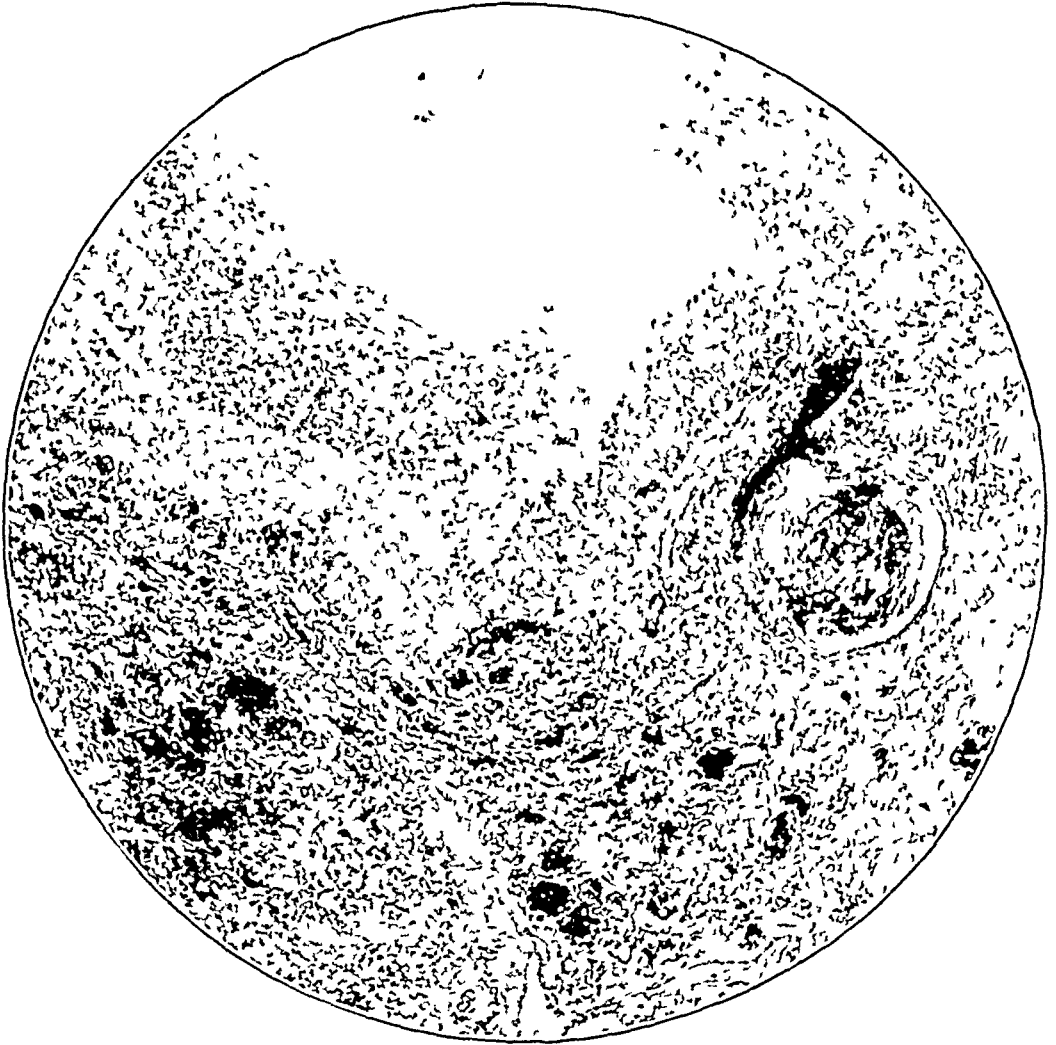


Fig 15—Low power photomicrograph of a portion of a bronchiectatic abscess, presumably the result of *Bacillus influenzae* infection A vein with a large thrombus undergoing organization is shown on the right of the abscess wall

from the appearance of mitosis in the epithelial cells and the presence of newly formed groups of epithelial cells which had not assumed the usual appearance of the older ones The hyaline membrane was quite resistant to the action of phagocytes or ferments, as it persisted apparently unchanged after the repair of the other elements of the virus lesion had begun In the later cases, this hyaline membrane was



In addition to the peculiar changes mentioned above, the alveolar spaces were in many instances markedly distended with air, so that adjacent lung tissue was compressed. Just what caused this distention was not evident, but it was assumed that the hemorrhage and hyaline material in some way acted as an obstruction to the outflow of air without preventing so effectively the inflow. In some instances, these alveoli were so distended that rupture occurred in the wall, and the

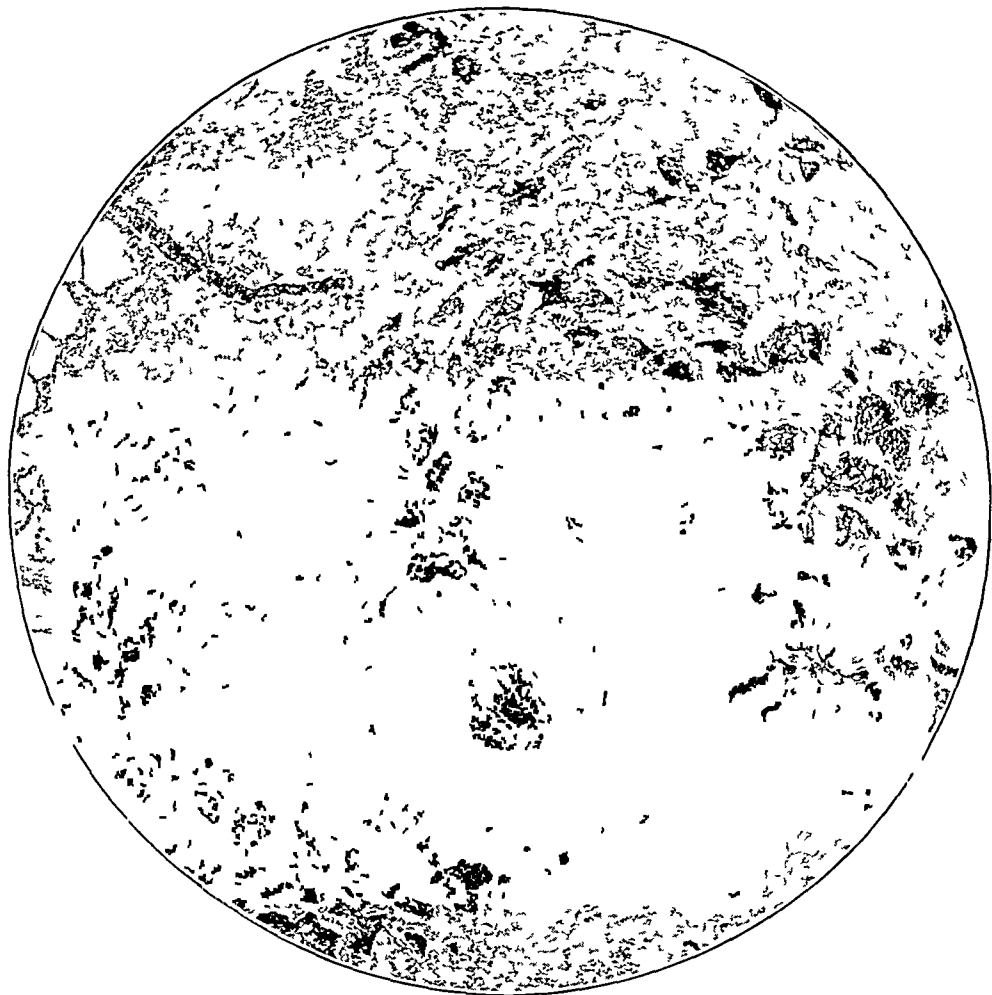


Fig 14—Low power photomicrograph of influenzal pneumonia followed by bronchitis and peribronchitis. The interstitial pneumonia and the fibrinous exudate into surrounding alveoli is well shown.

air extended into the adjacent connective tissue framework of the lung. As no extensive injury to the alveolar walls was seen in these cases, it was felt that the rupture of the air was purely mechanical.

In the early cases, few leukocytes or phagocytes were present with these various lesions, and it is not clear just what the next step in this reaction would have been had it remained uncomplicated. However, in all the cases in this group other organisms secondarily invaded the

tissue, but also the surrounding alveoli. The process consisted in congestion of the blood vessels with hemorrhage and the deposition of fibrin, necrosis of the epithelium lining of the alveoli and the presence of an inflammatory exudate through the supporting tissue and in the air spaces. This peribronchitis was seen in parts of the lung in which the virus lesion was not present as well as being superimposed on the



Fig 16—Photograph, about one-half the natural size, of a late stage of repair in influenzal pneumonia, in which the virus lesion has been followed by *Bacillus influenzae*, bronchitis, peribronchitis and bronchopneumonia. The alveolar emphysema persists. To be noted are bronchiectases of a large size completely surrounded in the middle portion of the figure by sclerosed lung tissue. The white patch at the apex shows an earlier stage of organization. The permanent character of the bronchiectases is particularly well illustrated in this photograph in the middle portion of the figure.

invaded by leukocytes and phagocytes and eventually organization with connective tissue took place into it. If some of this hyaline membrane had been removed by ferment action, no evidence of it was seen in these cases, but it seems reasonable to consider that such action may have been going on as well as the phagocytosis and organization. The emphysema of the alveolar spaces persisted to some extent in the patient who survived, but this lesion was more pronounced in the early days of the pulmonary involvement. Although frequently in the later stages the alveoli were distended, they usually were filled with exudate owing to the secondary invading organisms.

In one case an interesting condition was encountered in that in one part of the lung the old virus lesion was undergoing repair amid the lesions produced by secondary invading organisms, and in another part of the lung an early fresh virus lesion was found with all the usual histologic findings. This also has been observed by Goodpasture.<sup>2</sup>

Returning now to the actual processes going on in the lung owing not only to the virus of the epidemic disease but to the secondary invading organisms, a complicated pathologic picture was presented. The character of the lesions varied with the organisms found in the lung, thus, the pneumococcus superimposed the usual picture of a lobar pneumonia on this virus lesion, and if the virus lesion was not present in the particular lobe, there was the appearance of a straight lobar pneumonia. In the same way, in another case the hemolytic streptococcus produced its usual picture in the lungs in addition to the virus lesion. In other cases various unidentified organisms had invaded the lungs and produced local abscesses and even extensive gangrene. The details of the various lesions will not be discussed in this report, because they add nothing new to the existing knowledge of the pathology of such processes.

The invasion of the lung with the influenza bacillus, however, presented a pretty definite picture of interest, especially as it is possible that the virus lesion may eventually be attributed to this organism, and therefore what is about to be described may be simply additional processes due to the same cause. The exudative and infiltrative lesions considered to be produced by the influenza bacillus were not peculiar to that organism, as similar lesions have occurred in bronchopneumonia from the streptococcus and other causes.

In the smaller bronchi exudate was found consisting of polymorphonuclear and mononuclear leukocytes, in addition to red blood cells. These leukocytes were apparently attracted to the lumen of the bronchi by the bacteria or some toxin such as influenza bacilli and other organisms were found both free and intracellular in the lumen of these small bronchi. The process extended laterally from the lumina of the bronchi into their walls and involved not only the adjacent

In these lesions, hemorrhage was a conspicuous factor, and even as the lesion began to repair evidence of fresh hemorrhage was frequently found. It was felt that these red cells broke out of the vessels as part of the lesion about the bronchi and were not just the hemorrhage that remained from the virus lesion. It was one of the interesting features of these lungs that along with the process of repair the acute process was still actively going on. With this acute inflammatory reaction in and about the bronchi, the lumen of the bronchi often became dilated, and this dilatation of the bronchi in some instances remained after repair had taken place, and a condition of chronic bronchiectasis resulted.

As early as the twelfth or thirteenth day after the onset of the epidemic disease, evidence of repair of this bronchitis and peribronchitis began to appear. The epithelium in the bronchi and alveolar walls regenerated. Organization took place into the fibrin in the alveolar spaces and wherever it was deposited. Organization also occurred in the lymphatics and in the thrombosed vessels. There was nothing special in regard to the character of the organization. In some of the later cases certain of the smaller bronchioles were seen with a fresh epithelial covering over the underlying new connective tissue and the bronchiole permanently enlarged.

In summarizing the description of the lung lesions one may say that in the lungs on gross inspection the hemorrhagic appearance of the cut surface, the alveolar emphysema and in some instances the interstitial emphysema demonstrated the presence of the virus lesion. Dilated and prominent bronchi with a confluent bronchopneumonia emphasized the presence of the influenza bacillus lesion superimposed. Variable pictures of lobar pneumonia, patchy pneumonia, abscesses and gangrene showed that other organisms of various sorts were present. These findings were confined to one lobe or scattered throughout, or, as appeared in one case, various lesions appeared in the different lobes. Microscopically, the virus lesion could be separated from the lesions produced by other organisms and followed through its various phases. In addition, the inflammatory reaction to the influenza bacillus formed a fairly characteristic picture, and the picture produced by other organisms such as the pneumococcus and the streptococcus was as it usually is found.

Tissue from higher up in the respiratory tract was not preserved in many of the cases, but in those in which sections of the larger bronchi and trachea were studied the process was one of injury and desquamation to the epithelium with congestion and cellular reaction in the subepithelial layer and connective tissue. In some instances, the invading cells were polymorphonuclear leukocytes, in other mononuclear cells of the lymphocytic series.

virus lesion, and therefore was considered to be due to the influenza bacillus or some other organism irrespective of the virus. As this process extended laterally, blood vessels and lymphatics became involved. An acute inflammatory reaction in the arterial walls was seen in some cases with a fibrin deposit, necrosis of the walls of the vessel and cellular infiltration. Thrombosis was found in the blood vessels, and the lymphatics were distended with various types of

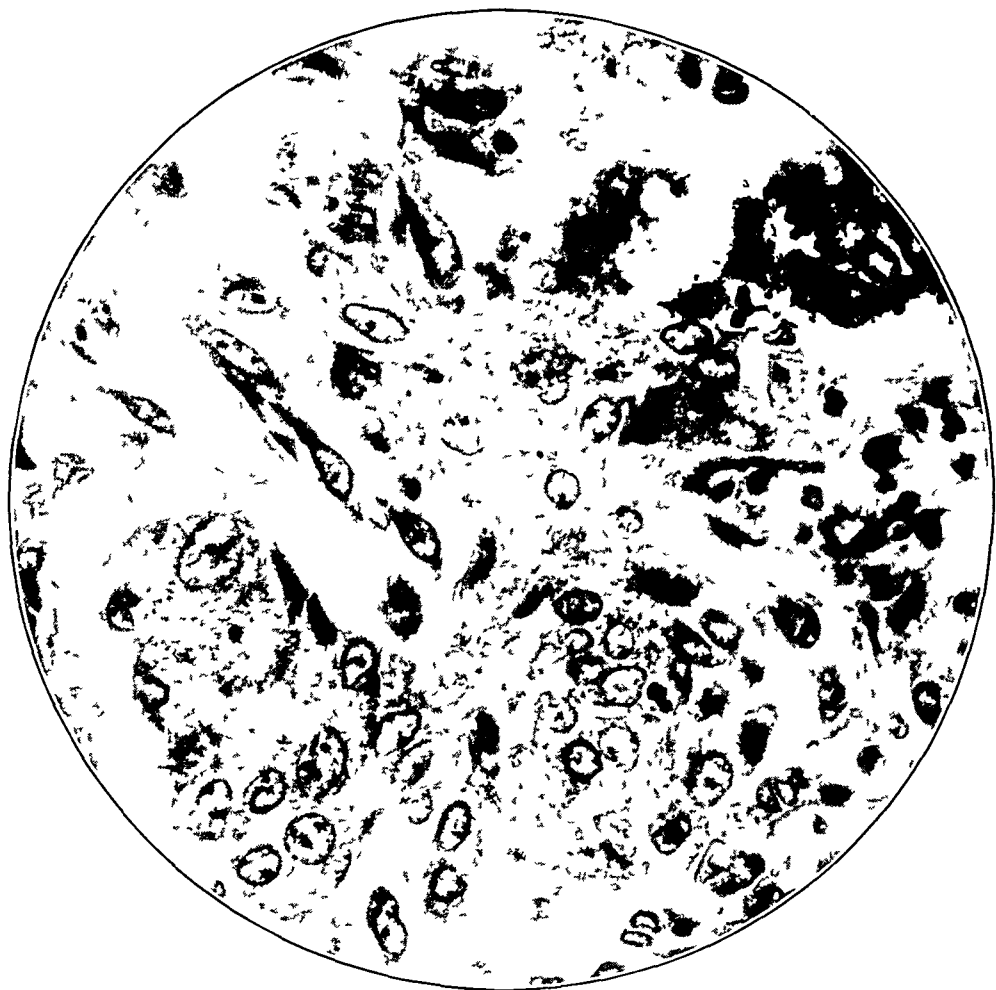


Fig 17—Photomicrograph of about 700 diameters showing the excessive regeneration of epithelium in atelectatic alveoli in the repair of the virus lesion. This epithelial regeneration is an almost invariable accompaniment of repair when organization occurs.

leukocytes and phagocytic cells. This thrombosis in the blood vessels in the peribronchial lesions plays an important part in the fate of the exudate in the parts of the lung supplied by these vessels and probably accounts for the necrosis and organization which was often seen.

# OBSERVATIONS ON CHANGES IN THE SIZE AND SHAPE OF HEARTS DURING THE PROGRESS OF COMPENSATION \*

I C FRIEDMAN, M D, AND SIDNEY STRAUSS, M D

CHICAGO

The general impression prevails that considerable variation in heart size is a not infrequent occurrence in pathologic conditions, and that such variations are indicated by variation in position of the apex beat due to left ventricular involvement. This, however, is not borne out by the few definite statements which could be found in the literature. Mackenzie states that during the progress of compensation no appreciable difference in heart size could be detected. Hoffman<sup>1</sup> states that in chronic heart disease compensation may or may not be accompanied by change in size and that size in itself is no certain indication of functional capacity, that being determined by muscle tonus. Martin<sup>2</sup> cites a case in which teleoroentgenograms during the convalescence from pneumonia showed a diminution in size of the heart. Vaquez<sup>3</sup> illustrates a case of myocarditis showing progressive retraction of all borders during intravenous injections of strophanthin. However, the extent of such changes is not indicated except in Vaquez' case, in which it amounted to 27 cm. It was this lack of exact data that prompted us to make this study.

The differences of opinion on this subject are probably partly due to the large personal factor in the percussion of heart borders. It was decided, therefore, to percuss the heart outlines of patients with decompensated chronic lesions at various times during their stay in the hospital, note the borders so obtained with lead markers, and control such determinations by teleoroentgenograms in order that the percussion errors might be visualized and more exact data of the heart size obtained. In the examination of roentgen-ray films, two main points were determined. First, the so-called transverse diameter of the heart, and, second, the heart outline. The transverse diameter is usually defined as the sum of the greatest distance of the right and left borders from the median line, commonly designated *ML* and *MR*. It seems to be well established that this diameter taken in conjunction with the

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\* From the Investigative Service, Medical Department, Michael Reese Hospital.

1 Hoffman. *Erkrankungen des Herzens*, 1911, p. 277.

2 Martin. *Am Jour Rontgenol* 8:295, 1921.

3 Vaquez and Bordet. *Heart and Aorta*, translated by Albert Honey and John Macy, Yale University Press, 1920, p. 63.

## CONCLUSIONS

From this study we have drawn the following conclusions. The cause of the influenza epidemic has not been established. The influenza bacillus is one of the secondary invading organisms. The virus which causes the epidemic, in addition to the general febrile reaction, the general toxic symptoms and involvement of the upper respiratory tract, produces in the lungs in a certain percentage of the cases characteristic lesions which we believe are pathognomonic of this disease.

The hyaline membrane in alveolar ducts and alveoli of the lungs is an effect produced by air forced into exudate.

The virus which produces the epidemic may also be responsible for Zenker's degeneration in muscle, a degenerative lesion in the cortex of the suprarenal gland and an injury to the tubules of the testicle, but we cannot exclude the effect of the influenza bacillus as a contributing factor in the production of these lesions.

All cases which terminated fatally were complicated by invasion with bacteria of which the influenza bacillus was the most frequent so that it is impossible to decide what the course of the virus lesion would have been if uncomplicated.

The pulmonary lesion due to the virus of the epidemic can be detected in the presence of superimposed secondary pulmonary infections.

The alveolar emphysema leads to rupture of the alveoli, interstitial emphysema, and finally escape of air into the subcutaneous tissues of the body. It is not established whether this would happen without secondary infection.

The pneumococcus and streptococcus produced in the lungs in the presence of the virus lesion their usual pathologic picture. *Bacillus influenzae* in these cases was responsible for the production and maintenance of a characteristic combination of bronchitis, peribronchitis, bronchiectasis, and bronchopneumonia.

is not always coincident with the apex as determined by the roentgenogram. This difference is present when the heart has become enlarged sufficiently to reach the lateral chest wall posterior to the anterior angle of the ribs. Here the marker will always lie outside the roentgen-ray position of the apex by a distance equal to the thickness of the chest wall, a considerable distance in fat or muscular people (Fig 6, seventh left interspace). Moreover, if the heart enlarges beyond this point, the apex can no longer move outward, since it has already reached the lateral chest wall and must therefore move backward and lie



Fig 1 (H B, Table 3) —Markers showing sources of error in percussing right heart border

obliquely in the chest cavity. When this occurs, an anteroposterior distance plate, being simply a projection of this obliquely placed heart, must have a somewhat smaller transverse diameter than the heart itself. Both methods then are liable to error in greatly enlarged hearts.

Group B (Table 2) includes those patients who left the hospital with hearts more or less compensated, but with the heart outlines the same as on entrance. This included seven cases, three of which are also classed in Group (c) on different admissions. There was one diagnosed myocarditis and six mitral lesions. The improvement in



heart outlines furnishes the most reliable evidence as to changes in heart size. It is also of value to determine the diameter in the second or third interspace.

In all twenty-one cases of decompensated chronic endo- and myocarditis were observed during one or more periods in the hospital. Of these, eleven patients had mitral lesions, one, aortic insufficiency, and nine, myocarditis. These cases all presented the usual clinical features of failure of the right side of the heart occasionally combined with failure of the left side of the heart. For purposes of comparison they were further divided into three groups:

(a) Those leaving the hospital unimproved and whose heart outlines remained unchanged.

(b) Those leaving the hospital with hearts more or less compensated, with heart outlines unchanged.

(c) Those leaving the hospital improved and with heart outlines changed.

Under group (a) (Table 1) were four cases, three of primary myocarditis and one of primary mitral lesion. As stated above, successive roentgen-ray plates of these patients superimposed on each other showed practically identical outlines in spite of variations in the transverse diameters up to 1 cm. The table shows also that, in the main, percussion figures and roentgen-ray measurements agreed fairly well, there being a difference of from 0.7 cm to 1.6 cm between the two, as a rule, the percussion figures were the lower. There is, however, one striking exception. This was in the case of R. R., in whom on entrance the transverse diameter, according to percussion, was 23.5 cm and the roentgen-ray measurement 18.9 cm. Had there been no control of percussion here, this would have been looked on as a case of marked diminution in size of the right side of the heart. It is well to note here the possible errors involved in determining slight changes in heart size by percussion alone. First, as to the right border. In using the lightest or threshold percussion, one often finds especially in decompensated hearts a change of note, that is, a rise in pitch, about 1.5 cm to the right of the true heart border, when percussing from without toward the heart border. This is indicated in Figure 1 by the outer of the two lead markers. This change in note often coincides with a dense hilus shadow. In order to determine the real heart border, one must continue the percussion until the change of note is accompanied by a feeling of resistance in the pleximeter finger tip. This is indicated in the illustration by the second marker. As the maximum retraction of the right border in our roentgen-ray controlled cases was 2.5 cm, it can be seen of what great importance this single error may be. The left border can, of course, be determined best by the position of the apex beat. However, the apex beat as determined by palpation

subjective symptoms was marked. Objectively, there was diminution of dyspnea and of cyanosis, somewhat lessened liver swelling and edema, in some marked slowing of the pulse and in two cases a change from fibrillation to sinus rhythm. Functionally, however, the improvement was only moderate, and one patient returned to the hospital in a short time with decompensation. The heart outlines in the patient with myocarditis are reproduced in Figure 2 (C H Table 2). This case was included in the group despite the fact that there was a slight change in heart outlines, for reasons given later. The technic used in obtaining the composite plates in the illustrations was to superimpose different



Fig 2 (C H, Table 2)—Slight increase in heart size with cessation of tachycardia

plates upon one another, using two fixed points, such as the junctions of the transverse processes with the tubercle of the first rib. The arch of the aorta and the lateral chest walls also served as checks in superimposing plates. In this manner, heart outlines of any number of films may be drawn on a single one, for purposes of comparison. The dotted line in this figure represents the condition at discharge, at which time the fibrillation and tachycardia had ceased. It will be seen that not only was there no retraction of the borders, but slight movement of the left border outward (0.9 cm). It is believed by some that a cessation of paroxysmal tachycardia is accompanied at times by

TABLE 1—*Patients Leaving Hospital Unimproved with Heart Outlines Unchanged*

Name	Age	Lesion	Decom- pensation	Improve- ment	Dates	Cardio- thoracic Ratio	Percussion Measure		Roentgen Ray Measurements		Urine, O c	Pulse	Remarks	
							Right	Left	Total	Right	Left	Total		
D F	57	Myoe iriditis, hyper- tension and heart block	No		10/16/22 10/30/22	0.56	3 4	11 11.5	14 15.5	4 5.1	10.2 9.7	14.2 14.8		Considerable haziness in lungs in first plate, second much clearer
R R	53	Myocarditis tortitis, hypertension, electro- cardiogram showed slight arborization block	Yes	No	11/25/22 12/12/22 1/18/23	0.71	9.0 5.4 6.0	14.5 12.6 13.7	23.5 18.0 19.7	5.7 6.5 7.4	13.2 12.2 10.5	18.9 18.7 17.9	100-114 80	No change
L H	48	Myocarditis and fibrillation	Marked	Very slight	9/ 8/22 10/24/22	0.69	5.0 5.8	16.0 14.7	21.0 20.5	6.5 5.5	12.2 12.2	18.7 17.7		No changes except in the region of conus pulmonalis
M C	46	Double mitral current or fibrillation	Yes	No	10/17/22 11/ 6/22 11/22/22	0.66	5.5 4.0 4.5	11 11 11.5	16.5 15.0 16.0	6.0 4.7 7.5	10.4 11.9 9.8	16.4 16.6 17.3	90 irreg 60-84 irreg 60 irreg	No change

an increase in heart size due to greater filling during diastole. The pulse rate of the patient mentioned in the foregoing on entrance was 140 to 152, on discharge 52 to 64. In another case (M O, Table 2) in which the slow fibrillation (72 to 80) gave place to sinus rhythm with a pulse rate of 72, there is no change in position of the left border. In three patients belonging to group (c) fibrillation ceased during the period of observation. In the first patient (B G, Table 3), when sinus rhythm was restored there was slight retraction of the left border and of the left auricle and superior vena cava of the right border. In the second (I B, Table 3), fibrillation began again during the early part of her stay in the hospital. At this time there was a movement outward of all borders. On the second cessation of fibrillation, the borders again clearly retracted. In the third case (B W, Table 3), there was no change of borders on the cessation of fibrillation. To sum the matter up, there is apparently no fixed rule for change in heart size or shape when fibrillation ceases. All borders may become smaller or remain unchanged. Considering the percussion figures alone in this group we would have diagnosed a diminution in size of the heart on discharge in every case but two. As a rule, the percussion figures for the transverse diameter were 1 to 2 cm greater than the roentgen-ray figures. Probably the limit of error in percussing the transverse diameter is 2 cm.

Group (c) (Table 3) includes the remaining cases, namely, patients leaving the hospital improved and with heart outlines changed. There were thirteen in this group, including three already considered in other groups on different admissions. There were five cases of myocarditis, seven of mitral lesions and one of aortic insufficiency. Subdividing these again according to the heart divisions which showed a change during compensation, we find seven cases which showed retraction of all borders including the superior vena cava and pulmonary artery, four cases improved with retraction of the right border alone, one case showed retraction of the left border alone (on one admission) and two cases showed retraction of great vessels alone. An illustration of retraction of all borders including the great vessels in a case of myocarditis is given in Figure 3 (M A of Table 3). It will be noticed that the diminution involves the following curves: first, the upper right curve extending in this figure to the third interspace, that is, the border of the superior vena cava, second, the lower right curve from the third interspace to the cardiohepatic angle, the curve of the right auricle, third, middle left curve from the third rib to the fifth interspace, that is, the curve of the pulmonary artery, and fourth, the lower left curve or that of the left ventricle. The diminution in diameter of the base of the heart at the level of the third interspace (through the great vessels) is 1.5 cm. The diminution in the usual transverse diameter,

TABLE 2—Patients Leaving Hospital with Hearts More or Less Compensated with Heart Outlines Unchanged

Name	Age	Lesion	Decompensation	Improvement	Dates	Cardio- thoracic Ratio	Percussion Measure	Röntgen-Ray Measurements	Urine, C c	Pulse	Remarks
C H	38	Myocarditis, aortic stenosis and insufficiency fibrillation	Pain and palpitation	Yes, fibrillation ceased, pulse slow	1st admission 7/1/22 2d admission 10/30/22 11/6/22 11/28/22	0.61	Discharge 7.3 11 = 18.3 6.5 10 = 17.0 5.4 11.7 = 11.1	Right Left Total 6.5 10 = 16.5 6.5 9.5 = 16.0 7.9 8.5 = 16.4 6.6 10.1 = 16.9	240+	60-80 140-152 68-80 52-64	No change
A F	44	Double mitral	Slight, liver not enlarged, edema absent	Slight	10/11/22 10/26/22	0.64	4 12 = 16 3.3 10.7 = 14	5.2 9.2 = 14.4 1.5 10.5 = 15.0	510	96-120 (in bed) 84-100 (up)	No change
M O	45	Mitral stenosis and insufficiency, myocarditis	Moderate cyanosis and edema, precordial pain	Yes, but some distress remained fibrillation ceased	1/24/23 2/2/23 2/8/23	0.69	4.8 12 = 16.8 5.0 10.5 = 15.5 5.5 11.3 = 16.8	5.8 9.8 = 15.6 5.9 10 = 15.9 4.8 10.6 = 15.4	900 480 480	72-80 fibrill 68-84 73 reg	No change
B B 1st admission	40	Double mitral and fibrillation	Present, liver 3 finger below, no edema	Yes	11/23/22 12/10/22	0.62	3.7 9.5 = 13.2 1.7 11.0 = 15.7	6.6 11.2 = 17.8 6.2 11.7 = 17.9	650	96 irreg 80-84 irreg	No change
B W 4th admission	28	Double mitral	Moderate dyspnea, less dyspnea, liver still enlarged and tender on discharge	Yes, fibrillation ceased	1/25/23 2/14/23 2/20/23	0.67	5.5 12.5 = 18 6.2 13 = 19.2 5.3 12.5 = 17.8	7.0 12.3 = 19.3 6.9 12.4 = 19.3 7.1 12.0 = 19.1	540	80-100 72 reg	No change
E L 2d admission	32	Double mitral fibrillation	Yes	Slight	1/27/23 2/26/23	0.74	6 14.5 = 20.5 5 13.1 = 18.1	5.5 13.2 = 18.7 6.4 12.2 = 18.6			No change
B T	45	Double mitral fibrillation	Yes	At discharge first time	4/21/22 6/30/22	0.75	7 12 = 19 4.5 12.5 = 17.0	7.5 12.0 = 19.5 6.9 13.0 = 19.9	540 1,500		No change

H C	22	Double mitral fibrillation	Yes	Yes	11/18/22 12/ 6/22	0 77	7 1 6 5	16 7 == 24 1 10 7 == 23 2	10 8 4	11 0 == 24 0 11 4 == 22 8	1,740 1,260	130 apex 72	Marked diminution in size right border especially due to retraction of portion of left auricle projecting beyond right, slight retraction of pulmonary artery
B W	28	Double mitral disorder 2d admission After second discharge 3d admission	Dyspnea pain, liver 4 fingers below, no edema Slight dyspnea 1 liver 2 fingers below Still dyspnea, working part of the time, does not feel well Slightly more dyspnea	Yes	2/ 8/22 6/ 6/22 11/16/22 12/25/22	0 67	7 0 6 0 4 2 5 5	12 5 == 19 5 12 5 == 18 5 12 6 == 16 8 12 5 == 18 0	5 5 6 7 5 6 5 9	12 2 == 17 7 12 0 == 18 7 12 3 == 17 9 13 == 18 0	640 800 80 reg	152 irreg 76-80 reg 80 reg	Diminution in size of right border, especially superior vena cava and right auricle
B G	27	Double mitral fibrillation	Moderate, liver 4 fingers below, not tender, no edema	Subjective, with quinidin, sinus rhythm	10/24/22 11/ 8/22	0 65	5 3 4 0	10 8 == 16 1 10 7 == 14 7	Trans diam 3d space 10 4 6 8 5 9 Trans diam 3d space 8 3	870	88 60	Retraction of right border due to diminution in size of left auricle and superior vena cava, no change in transverse diameter, diameter in third space diminished 2 1 cm	
I B	45	Double mitral fibrillation	Slight	Yes, fibrillation ceased	9/ 0/22 10/ 3/22 11/24/22	0 62	2 5 3 5 3 0	10 0 == 12 5 10 5 == 11 0 10 2 == 13 2	4 0 4 8 4 2 Trans diam 2d 6 5	88 == 12 8 83 == 13 1 80 == 12 2	850	76 reg 72 irreg norm and reg	Retraction of both borders
B B 2d stay in hosp	40	Double mitral fibrillation	Yes	Yes	1/13/23 1/19/23 2/ 5/23	0 73	5 3 5 0 4 5	13 5 == 18 8 11 8 == 16 8 9 5 == 11 0	7 3 7 2 4 9	11 6 == 18 9 10 9 == 16 1 11 2 == 16 1	1,110 900	92-80 irreg 64 irreg 72 irreg	Marked retraction of right border, slight of left, diminution in third space 2 3 cm
M K	22	Double mitral and aortic	Yes, pain marked, liver tender and 3 fingers below	Yes, dyspnea and pain less, liver barely palpable	1/28/23 2/ 2/23 2/12/23	0 74	7 3 5 3 4 5	12 4 == 19 7 13 0 == 18 3 13 5 == 18 0	7 8 7 2 6 1	10 9 == 18 7 10 7 == 17 9 11 4 == 17 5	900 750 1,320	64-84 reg 72-92 reg 76-92 reg	Diminution in size of right auricle and superior vena cava, slight retraction of left auricle and pulmonary artery returning to typical aortic insufficiency outlines
E L 1st admission	32	Double mitral fibrillation	Yes	Yes	12/ 8/22 12/20/22 1/13/23	0 73	4 2 5 5 5 5	14 5 == 18 7 13 0 == 18 5 14 0 == 20 1	6 1 6 2 6 0	12 8 == 18 0 13 1 == 19 3 13 3 == 19 3	1,700 100 (diuretic)	80-94, irreg 80-84 irreg 70-88 irreg	Retraction only of pulmonary artery, 0 4 cm

TABLE 3—*Patients Leaving Hospital Improved with Heart Outlines Changed*

Name	Age	Lesion	Decompen- sation	Improve- ment	Dates	Cardio- thoracic Ratio	Percussion Measure		Roentgen Ray Measurements		Urine, C c	Pulse	Remarks
							Right	Left	Right	Left	Total		
H B	53	Myocarditis, chronic bron- chitis	Yes, dyspnea and edema, cough for 20 years	Yes	1/12/22 1/20/22 11/15/22	0.57	60 30 40	100 80 100	160 110 140	61 35 37	171 130 146	88-104 72-76 84 stand- ing	Retraction both borders, 4.1 cm
H S	65	Myocarditis, fibrillation, electrocardio- gram showed left prepon- derance and fibrillation	Yes	Yes	11/23/22 12/6/22 12/18/22	0.56	45 50 35	135 152 140	180 202 175	44 42 45	183 162 163	116 fibrill 60-70 64-88	Retraction left ventricle and superior vena cava
S C	50	Myocarditis, chronic interstitial nephritis	Yes	Yes	4/22/22 5/7/22 4/22/22 5/17/22	0.78	50 35	150 150	200 185	88 83	226 211	400 1,300	Retraction both borders especially superior vena cava and pulmonary ar- tery marked diminution of pulmonary edema hilum congested and in- creased sharpness of heart curves, diminution in transverse diameter 1.5 cm, in great vessels 2.4 cm
M A	62	Myocarditis, emphysema and arterio- sclerosis	Yes	Yes	1/5/23 1/23/23	0.508	45 33	107 94	152 127	46 45	151 129	84-116 60-84	Marked diminution in trans- verse diameter, especially pulmonary artery and right auricle
Mrs J	44	Myocarditis, fibrillation	Yes	Yes	12/4/22 12/16/22 1/9/23	0.78	58 55 50	115 135 125	173 190 175	? ? 73	125 120 122	112-126 103 apex 88 apex	Retraction of border of superior vena cava and pulmonary artery, no change in transverse diameter
V G 1st stay hosp	42	Double mitral	Marked edema	Decided	7/29/22 9/6/22	0.68	40 40	175 135	215 175	57 55	167 152	93-120 80-92	Retraction of left ventricle
2d stay in hosp		Same	Not so marked, slight edema, liver 4 fingers below arch	Marked	10/21/22 11/29/22	0.61	45 54	135 110	180 164	54 48	179 158	84-100 —	Retraction of both borders, diminution in diameter of great vessels, second inter- space, 3 cm

angle at the junction of the superior vena cava and the right auricle probably due to retraction of a projecting border of the left auricle. Second, after a further stay of two and one-half weeks, another film showed the left border unchanged and the right border markedly diminished involving this time the superior vena cava and the right auricle. The part played by the right ventricle in such a contraction is not accurately determined by this method. The total diminution in size of great vessels measured in the third interspace is 2.3 cm. The diminution in usual transverse diameter ( $ML$  and  $MR$ ) was 2.8 cm.



Fig. 4 (B. B., Table 3) —At first there was retraction of left border only, later of right border. The outer solid lines indicate condition on Jan. 13, 1923, the dotted lines on Jan. 19, 1923, and the inner solid lines on Feb. 5, 1923, left border coincides with dotted line.

The marked diminution in size of the great vessels compared with the change in the usual transverse diameter noted in Figure 4 and the preceding one was noticeable also in four other cases in this group. In one (V. G., Table 3) the diameter of the base diminished 3 cm., the transverse diameter, 2.1 cm. In another (S. C., Table 3) the diameter at the base diminished 2.5 cm., the transverse 1.5 cm. In two others, the decrease was either equal to or slightly less than that of the trans-



that is, through the widest points of the right auricle and left ventricle, is 22 cm To be noted is the relatively large change in the size of the superior vena cava and pulmonary artery

In Figure 4 (B B, Table 3) a double mitral lesion with fibrillation is presented On first admission, there was moderate improvement subjectively but no change in heart outlines (B B, Table 2) She

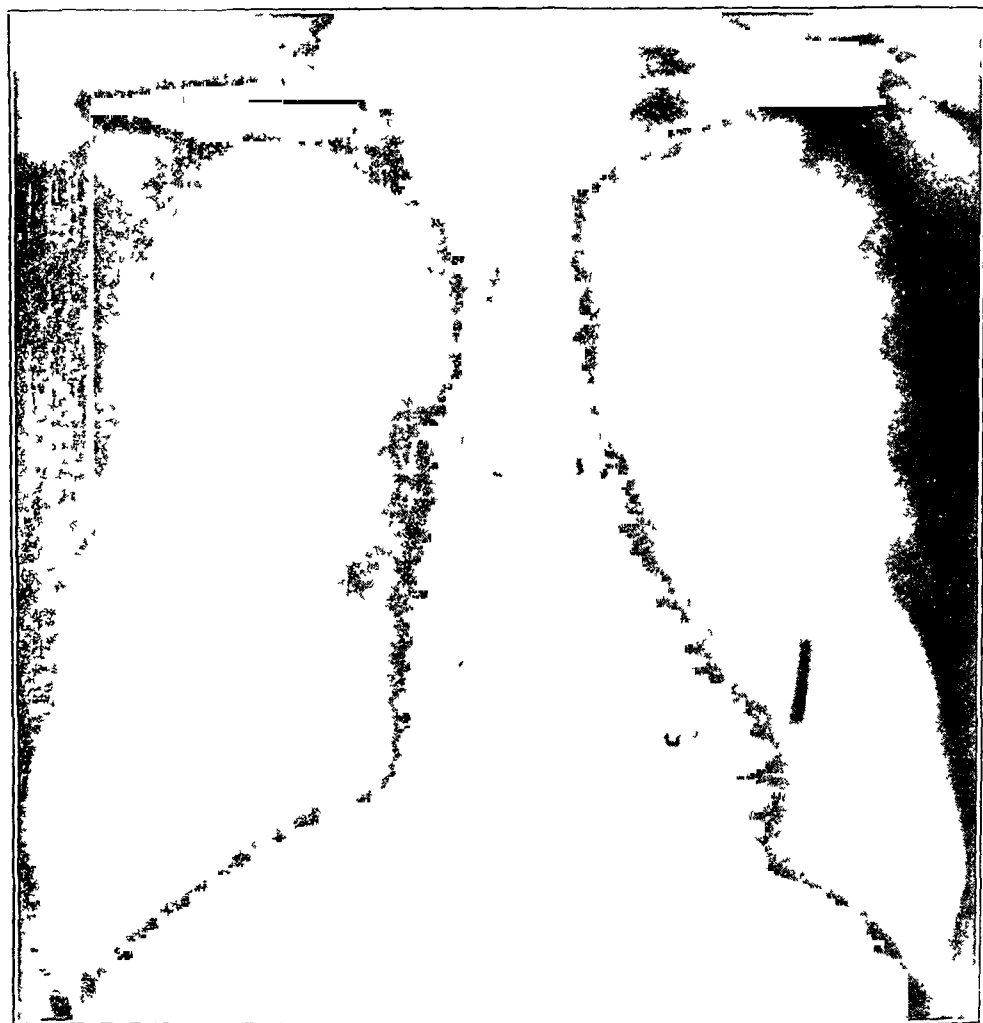


Fig 3 (M A, Table 3) —Retraction of all borders The solid line indicates the condition on admission Jan 5, 1923, the dotted line, on discharge Jan 23 1923 Note pulmonary artery and superior vena cava

returned in three weeks with decompensation, with the transverse diameter 1 cm greater than on the previous discharge The improvement during this stay was marked by two stages of retraction First, at the end of a week there was a retraction of the whole left border, especially marked in the region of the pulmonary artery, and a slight change in the contour of the right border, indicated by a more acute

the middle solid line, a distance of about 1 cm. The middle curve on the right side extending from the second to the fourth interspace is possibly due to a projecting left auricle. Periods of improvement, then, were marked by retraction of the right and left auricles and superior vena cava, the left border remaining unchanged, that is, reduction in size of the right and left ventricles was not a factor in producing com-



Fig 6 (H E, Table 3) —Change mostly in right border. The innermost dotted line on the right side does not indicate the change in heart size but the junction of an inner dense shadow and an outer lighter one.

pensation. Another point to be mentioned is the clearing up of lung detail in the last plates taken of this patient, as well as the increased sharpness of heart outline, both due to diminished engorgement and edema. In several other cases, the same points were noted. In one (D F, Table 1) there was no subjective improvement, no change in heart outline, and still a diminution of pulmonary edema.

verse diameter The average decrease in the diameter of the great vessels in group (c) was 1.5 cm, the average decrease in transverse diameter of the heart in this group was 2 cm The importance of this point lies in the fact that percussion of the borders of the heart base is quite unreliable (for example, marker in Fig 4) In contrast with this it will be noted from the figures in Table 3 that the percussion measurements of the transverse diameter of the heart agreed fairly well with the teleoroentgenographic measurements



Fig 5 (B W, Table 3) —Change in right border only Inner dotted line shows condition on Nov 16, 1922 The patient was ambulatory Outer solid line indicates condition on fourth admission, Jan 25, 1923 Middle solid line indicates condition on fourth discharge, Feb 20, 1923

Figure 5 (B W, Table 3) is an illustration of retraction of the right border alone The patient had a double mitral lesion with periods of fibrillation The plate in the illustration was taken when the patient was out of hospital doing light work On readmission, again because of decompensation with fibrillation, the whole right border had extended outward, indicated by the outer-most solid line After a stay of about four weeks, the right border again retracted to the area indicated by

interspaces, also due to the projecting left auricle. A similar change was noted in the discussion of B B (Fig 4). In another patient (M K Table 3), who had an aortic insufficiency, the change during compensation was also most marked in the right border, that on the left being limited to a slight retraction in the pulmonary artery region restoring the curve to the aortic insufficiency type.

In Figure 7 (V G, Table 3) is shown a double mitral disorder in which improvement on the first admission was accompanied by a retrac-

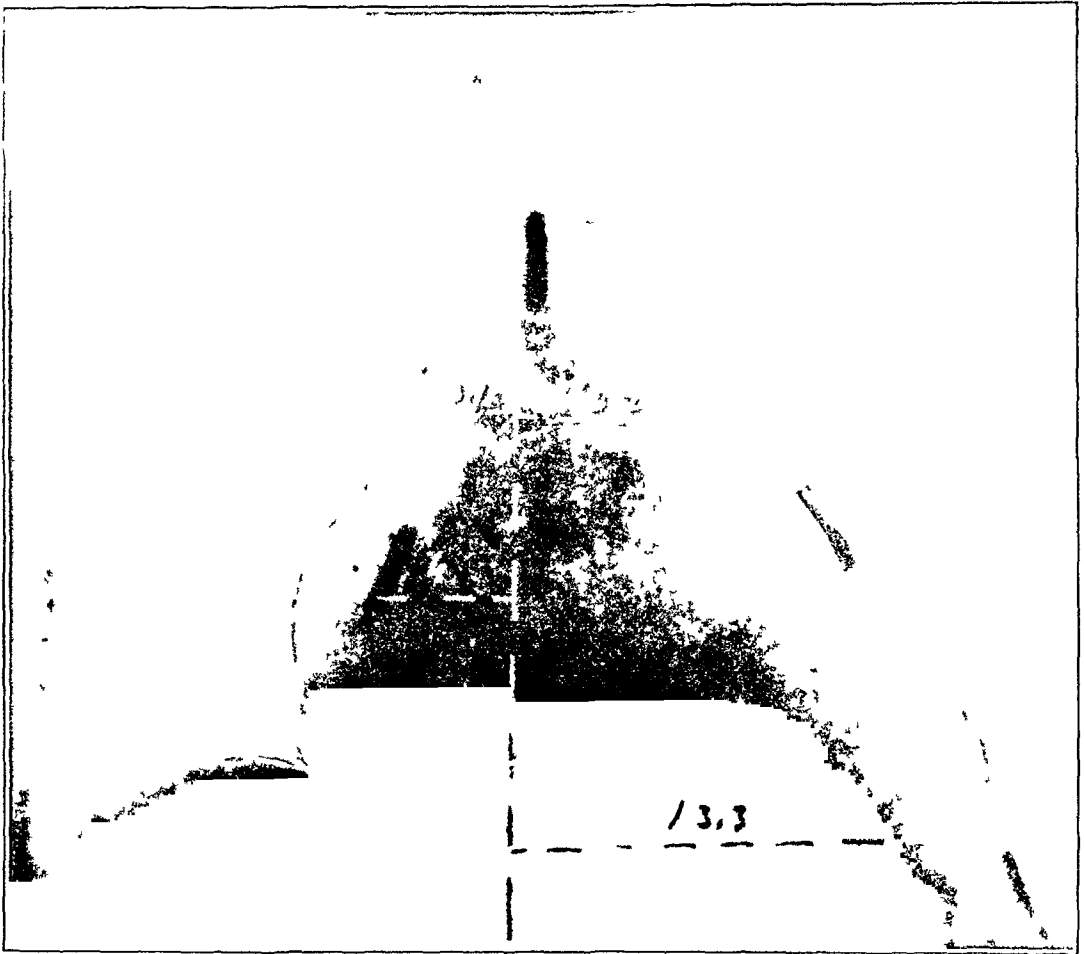


Fig 8 (E L, Table 3) —Marked retraction of distended pulmonary artery

tion of the left border only. This is the only case of the kind in the series. A point of interest in this patient is the fact that though decompensation was not so marked on second admission as on first, the heart was larger. It has, of course, often been pointed out that the size of the heart bears no necessary relation to its functional capacity. Another feature of this case is the fact that on a later admission improvement was accompanied by a retraction of all borders.

Figure 8 is an example of unchanged heart borders except in the area of the great vessels, here limited to the region of the pulmonary

In Figure 6 (H E, Table 3) a case of double mitral disorder with fibrillation, the greatest change is in the right border, especially in fourth and fifth interspaces. The most striking feature in the series of plates of this case is the lighter shadow projecting to the right of the innermost dotted line, evidently due to a greatly distended superior vena cava and right and left auricles. Improvement was indicated by retraction of this lighter shadow only, especially in the fourth and fifth interspaces. This is most probably due to retraction of the left

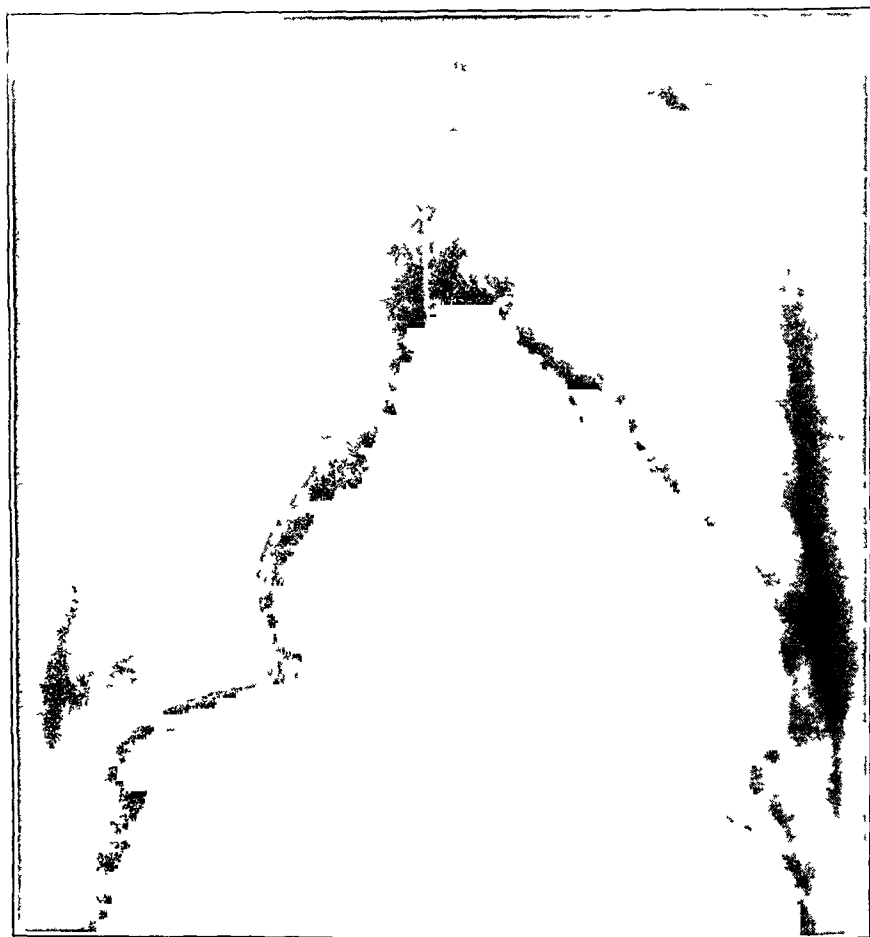


Fig 7 (V G, Table 3) —First admission, retraction of left border only

auricle, which in such cases projects from the posterior heart surface beyond the right auricle, as has been demonstrated by Assmann and Neumann. The darker shadow within the inner dotted line is due to the right ventricle which remained unchanged during compensation. There was a slight change in the pulmonary artery region, part of which may also be due to the left auricle retraction. B G, Table 3, belongs to this subgroup (retraction of the right border only). Here, too, the most striking feature was a retraction in the third and fourth right

# OBSERVATIONS ON THE INFLUENCE OF PITUITARY EXTRACT ON THE METABOLISM IN DIABETES INSIPIDUS \*

JAMES F WEIR, M D

ROCHESTER, MINN

The chief disturbance associated with diabetes insipidus relates to water metabolism, and in any discussion of the subject the changes induced in normal persons by drinking water copiously must be kept in mind. Voit<sup>1</sup> pointed out that there is a small increase in nitrogen elimination after copious water intake, although Straub<sup>2</sup> found no effect on nitrogen equilibrium of man following the extra ingestion of 2 liters of water. Heilner<sup>3</sup> found increased elimination of nitrogen in fasting dogs after the intake of 2 liters of water each day for two days. Hawk<sup>4</sup> gave more water and less protein to human beings and found that 4,500 c c of water each day raised the urine nitrogen from 11.03 to 12.48 gm on the first day, and to 11.82 gm on the second day, with a secondary fall to 10.91 gm.

Rosenbloom and Price<sup>5</sup> studied the metabolism of a boy, aged 4 years, suffering from diabetes insipidus. They found a normal amount and partition of urinary nitrogen. Increased protein intake was followed by increased nitrogen output. A low percentage of nitrogen was found in the stool, as compared with the nitrogen intake. They consider that the increased ingestion of water favors the absorption of nitrogen from the gastro-intestinal tract, which Hawk has shown lessens the amount of fecal nitrogen excreted. These authors believe that there is no important change in the state of nutrition or protein metabolism in this disease. The chlorine metabolism was normal, except that an increased sodium chlorid intake resulted in larger quantities of

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1 Voit, quoted by Lusk, G. Science of Nutrition, Ed 3, Philadelphia, W B Saunders Company, 1919, p 162.

2 Straub, W. Ueber den Einfluss des Kochsalzes auf die Eiweisszersetzung, Ztschr f Biol **19** 527-549, 1898-1899.

3 Heilner, E. Ueber die Wirkung der Zufuhr von Wasser auf die Stickstoff und Chloralasscheidung im Harn, Ztschr f Biol **47** 538-561, 1906.

4 Hawk, P B. Studies on Drinking Water, Univ Penn Med Bull **17** 7, 1905. Fowler, C C, and Hawk, P B. Studies on Drinking Water. II. The Metabolic Influence of Copious Water Drinking with Meals, J Exper M **12** 388-410, 1910.

5 Rosenbloom, J, and Price, H T. A Metabolism Study of a Case of Diabetes Insipidus, Am J Dis Child **12** 53-60 (July) 1916.

artery in the second and third interspaces. Though less marked at discharge, the projection in this area was still present. Although in only two instances of this series were the changes limited to the great vessels, as a part of right and left border changes, we have previously pointed out their importance.

In summing up groups (b) and (c) we find that in 35 per cent of patients recovering compensation, there was no diminution in the diameter of the heart or great vessel. In 35 per cent more there was diminution in all diameters. In the remaining 30 per cent, there were changes in one border only, most frequently in the right.

The diminution in great vessel diameter varied from 0.4 to 3 cm, that in transverse heart diameter from 0.8 to 4.1 cm.

### CONCLUSIONS

1 Cardiac compensation may be restored without any change in any diameter of the heart, with changes only in the great vessels, especially in the superior vena cava and pulmonary artery, with changes in the right or left borders or with changes in all borders. At times the change in the right border is due to the retraction of the projecting left auricle.

2 A total change of 1 cm in the transverse diameter is within the limits of roentgen-ray error. A change of less than 1 cm when accompanied by change of shape may have considerable significance.

3 Most striking is the slight change in the left border as compared with the right.

4 The most frequent change is that at the base, namely, the superior vena cava and pulmonary artery. This variation cannot usually be determined by percussion. Therefore variations in size in chronic heart conditions determined by percussion alone are unreliable.

5 In cases in which decompensation occurs more than once, different divisions of the heart may be affected each time, although the clinical pictures presented are identical.

6 In chronic heart disease there may be marked variation in function, with slight or no variation in size.

104 South Michigan Avenue

Leschke<sup>11</sup> studied two cases of diabetes insipidus under normal conditions and on restriction of fluids (thirst). His data would indicate a concentration of the blood in the latter condition.

Brunn<sup>12</sup> reports evidence of a hydremia after the administration of pituitary extract to patients with diabetes insipidus and to normal persons. The drug temporarily blocked the kidneys to water secretion. Konschegg and Schuster<sup>13</sup> found dilution of the blood after the administration of pituitary extract.

Priestley<sup>14</sup> investigated the effects in normal persons of drinking water copiously and found no change in the hemoglobin, or the oxygen content of the blood. The electrical conductivity was decreased. By the determination of the total solids and of the plasma chlorids, he demonstrated a slight dilution of the blood during the diuresis following ingestion of 2 liters of water. Administration of pituitary extract delayed the diuresis for from four to six hours, if it had already begun, the drug cut it short at once. The interference with absorption from the gastro-intestinal tract produced by the drug, as claimed by Rees,<sup>15</sup> is slight, and not sufficient to account for the prevention of this diuresis.

In general, it is agreed that increased water intake by normal persons results in a slight increase in the urinary nitrogen elimination, while the fecal nitrogen is diminished because of better absorption. It is likewise agreed that in cases of diabetes insipidus, a slight dilution of the blood serum occurs after the administration of pituitary extract. There is some difference of opinion with regard to the elimination of urinary nitrogen and chlorine in this disease before and after administration of the pituitary extract. However, no striking disturbance in the metabolism of these elements has been noted.

#### CLINICAL MATERIAL STUDIED AND METHODS UTILIZED

Comprehensive studies<sup>16</sup> were made of the blood and urine of two cases of diabetes insipidus (Cases 1 and 2). The studies in the second

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11 Leschke, E. Beiträge zur klinischen Pathologie des Zwischenhirns. I. Klinische und experimentelle Untersuchungen über Diabetes insipidus, seine Beziehungen und zur Hypophyse und zum Zwischenhirn, *Ztschr f klin Med* 87 201-279, 1919.

12 Brunn, F. Ueber diureschommende und diuretische Wirkung des Pituitrins, *Zentralbl f inn Med* 41 674-679, 1920.

13 Von Kónschegg, A., and Schuster, E. Ueber die Beeinflussung der Diurese durch Hypophysenextrakte, *Deutsch med Wchnschr* 2 1091-1095, 1915.

14 Priestley, J. G. The Regulation of the Excretion of Water by the Kidneys, *J Physiol* 55 305-318, 1921.

15 Rees, M. H. The Influence of Pituitary Extracts on the Absorption of Water from the Small Intestine, *Am J Physiol* 53 43-48, 1920.

16 These studies were completed by March, 1921, and preceded the publication of several of the articles mentioned in the references.



urine and no change in chlorin concentration in the urine. The metabolism of sulphur, calcium, phosphorus and magnesium was also normal.

Gibson and Martin<sup>6</sup> found a high level of ammonia and of undetermined nitrogen in the urine in a case of diabetes insipidus before the administration of pituitary extract, a considerable nitrogen retention with a lessened elimination and a more normal nitrogen partition after the administration of pituitary extract, and a return to the former condition as the effects of the drug disappeared.

Christie and Stewart<sup>7</sup> found a slightly decreased electrical conductivity of the blood of normal persons after the ingestion of large amounts of water, indicating a more dilute serum in respect to electrolytes, and, on restriction of fluids, a slight increase in the electrical conductivity of serum, and a corresponding decrease in volume relative to corpuscles. In a case of diabetes insipidus, after voluntary restriction of fluid intake or after pituitary extract administration, they found a definite but slight increase in the conductivity of the serum and a corresponding slight decrease in its volume, relative to the corpuscles. In a recent publication<sup>8</sup> these authors report similar studies in two further cases of diabetes insipidus, finding no definite changes in the electrical conductivity of the serum, or its percentage volume before and after water deprivation. Furthermore, there was no change, either one-half hour or five to six hours after resumption of water ingestion, other than a slightly greater percentage of serum in the specimen taken after five to six hours.

Williams<sup>9</sup> found sodium chlorid elimination in diabetes insipidus was on a higher plane after administration of pituitary extract.

Rabinowitch,<sup>10</sup> in the study of a case of diabetes insipidus, found a normal nitrogen balance, but hyperchloremia, and high salt threshold and salt retention. Sodium chlorid stimulated the kidney by lowering the threshold in proportion to the amount of the chlorid given. After pituitary extract had been given, there was increased salt excretion and concentration.

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6 Gibson, R. B., and Martin, F. T. Administration of a Pituitary Extract and Histamin in a Case of Diabetes Insipidus, *Arch Int Med* **27** 351-360 (March) 1921.

7 Christie, C. D., and Stewart, G. N. Study of a Case of Diabetes Insipidus with Special Reference to the Mechanism of the Diuresis and of the Action of Pituitary Extract on it, *Arch Int Med* **20** 10-23 (July) 1917.

8 Christie, C. D., and Stewart, G. N. Study of Some Cases of Diabetes Insipidus with Special Reference to the Detection of Changes in the Blood when Water is Taken or Withheld, *Arch Int Med* **29** 555-566 (May) 1922.

9 Williams, J. R. Diabetes Insipidus. A Metabolic Study of the Effect of Pituitary Administration, *Endocrinology* **1** 312-325, 1917.

10 Rabinowitch, I. M. Metabolic Studies on a Case of Diabetes Insipidus, *Arch Int Med* **28** 355-366 (Sept) 1921.

8 p m, July 7, to 8 a m, July 8), and in the period of treatment from 130 cc to 317 cc except for the period between 8 p m, July 10, and 8 a m, July 11, when the average three-hour excretion was 655 cc. At this time the effect of solution of hypophysis (Squibb) was apparently wearing off, since from 8 a m to 8 p m, July 9, the excretion was 862 cc, and for the same period on July 10, 774 cc, showing uniform action of the drug.

In the balance of water, nitrogen and chlorids (Table 3), the experiment is satisfactory, as the nitrogen and chlorid intakes were uniform. There was no diarrhea after the administration of the drug,

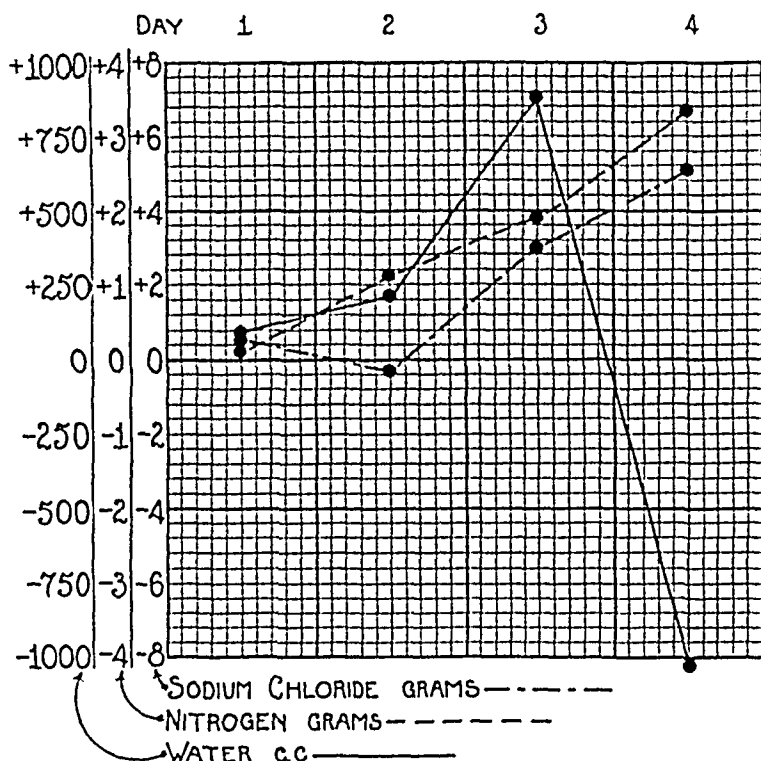


Chart 1 (Case 1) —Balance of water, nitrogen and chlorids during metabolism experiment

and analysis did not reveal increased elimination of these elements in the feces. The low water balance in the normal period calculated from water intake and output indicated unusually small losses by way of the skin and lungs, provided there was no change in weight. This harmonized well with the clinical observations of dry skin and mouth. The marked increase in the retention of water after the first dose of pituitary extract corresponded to the drop in urinary output. The negative balance on the last day, due to the large excretion of urine from 8 p m to 8 a m, when the effect of the drug had apparently decreased, suggested that the water had been retained. The excretion of nitrogen in the urine was not greatly changed on the first day of treat-

case were repeated during the patient's subsequent admission to the hospital. Studies of the blood were made in two other cases (Cases 3 and 4) and in normal persons. An attempt was made to ascertain changes in the metabolism and excretion of water, nitrogen and chlorids during the administration of pituitary extract and variations in the composition and volume of the blood incident to these changes. All of the subjects were under careful control in the hospital. Freedom of water intake was allowed, but the amounts were carefully measured. A constant diet was maintained and some of the articles of food were analyzed for total nitrogen and sodium chlorid. Pituitary extract, when given, was injected sufficiently often to insure continuance of action. Great care was taken in the collection of specimens, and duplicate analyses were made as follows: Total nitrogen of urine, plasma, feces and food, Kjeldahl method, urine chlorids, Volhard method, blood chlorid, Rappleye method, food chlorids by Volhard's method after ashing, urea, creatinin, uric acid in urine and blood, according to the methods of Folin and Wu, urinary ammonia, Malfatti method, urinary acidity, titration with 0.1 normal alkali, total nonprotein nitrogen, Folin's method, blood sugar, Benedict's method, molecular concentrations from depression of the freezing point; relative plasma volume by the hematocrit, and water content of feces by drying to a constant weight.<sup>17</sup>

#### EFFECTS OF PITUITARY EXTRACT ON METABOLISM OF WATER, NITROGEN AND CHLORID IN TWO CASES OF DIABETES INSIPIDUS

CASE 1—Mr C. N. N., aged 47 years, came to the Clinic on April 23, 1920. He had had typhoid at the age of 12 and a syphilitic infection at the age of 24. In June, 1914, he had had pain in the legs and a sudden onset of polydipsia, polyuria and weakness. In 1915, he had had transient attacks of diplopia. His weight increased to 220 pounds (99.7 kg), but this lasted only a few months. For the last five years there had been slight incontinence of urine. Libido and potentio had been progressively and persistently diminishing.

At the time of examination, the patient weighed 175 pounds (79.3 kg). His pupils reacted slowly to light and to accommodation, and were irregular. Incoordination and Romberg's sign were present. The patellar and Achilles reflexes were absent. There was loss of vibration, position and pressure sense. A diagnosis of syphilis of the central nervous system (parenchymatous) was made.

#### RESULTS OF OBSERVATIONS IN CASE 1

The water intake for each three-hour period before treatment varied from 720 to 1200 c.c., and under treatment, from 0 to 480 c.c. In the period before treatment the water output in the urine for three hours alone varied from 544 c.c. to 980 c.c. (average of specimen from

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<sup>17</sup> Water balance, as referred to here, is the difference between water intake and urine output. The water content of the food calculated from the tables of Atwater and Benedict, but not the water of oxidation, is included in the figures for the water intake.

TABLE 2—Uriney Partition During a Metabolism Experiment Before and After Administration of Pituitary Extract (Case 1)

Time	Volume, C c	Specific Gravity	Acidity, C c Normal Acid	Sodium Chloride, Gm	Total Nitrogen, Gm	Urea Nitrogen, Gm	Ammonia Nitrogen, Gm	Creatinin Nitrogen, Gm	Uric Acid Nitrogen, Gm	Urea Nitrogen, per Cent	Ammonia Nitrogen, per Cent	Creatinin Nitrogen, per Cent	Uric Acid Nitrogen, per Cent
July 7, 1920													
8-11	802	1.005	11.0	2.38	1.14	0.03	0.03	0.07	0.02	81.5	2.9	7.8	2.0
11-2	712	1.006	11.2	1.37	1.15	1.02	0.03	0.06	0.02	88.9	2.8	5.3	1.9
2-5	823	1.006	26.3	1.00	1.26	0.08	0.04	0.06	0.02	77.8	3.7	4.9	1.6
7-8	721	1.006	27.7	1.06	1.12	0.91	0.05	0.05	0.01	81.5	3.3	4.9	1.3
8-8	3,914	1.004	103.3	8.53	4.71	1.69	0.17	0.25	0.07	78.5	2.5	5.4	1.5
Total	7,032		189.5	17.89	9.8	7.73	0.32	0.49	0.15				
July 8, 1920													
8-11	544	1.005	12.9	1.27	0.80	0.79	0.03	0.05	0.01	73.8	3.6	6.8	1.6
11-2	735	1.005	7.0	1.32	1.05	0.91	0.01	0.06	0.02	86.7	1.1	6.1	1.5
2-5	830	1.007	83.7	1.35	1.27	1.05	0.06	0.07	0.02	83.1	1.6	5.7	1.3
7-8	808	1.006	20.0	1.88	1.13	0.93	0.05	0.07	0.01	82.0	1.0	5.9	1.3
8-8	3,840	1.006	62.3	9.62	1.23	1.17	0.18	0.27	0.06	81.9	4.3	6.3	1.3
Total	6,767		197.8	17.64	8.48	6.95	0.36	0.72	0.12				
July 9, 1920													
8-11	248	1.009	5.2	1.83	0.56	0.46	0.03	0.04	0.01	83.1	5.0	7.9	1.8
11-2	317	1.013	10.8	2.28	1.19	0.93	0.04	0.07	0.02	78.5	3.4	6.5	1.5
2-5	147	1.013	11.0	1.02	0.78	0.48	0.02	0.04	0.01	87.0	3.6	6.8	1.2
7-8	180	1.014	18.4	0.91	0.77	0.65	0.03	0.05	0.01	84.6	1.2	6.0	1.2
8-8	1,080	1.014	156.9	6.47	7.21	1.76	0.16	0.32	0.07	83.6	3.1	6.1	1.3
Total	1,942		171.3	12.51	8.31	6.88	0.38	0.52	0.11				
July 10, 1920													
8-11	130	1.014	0	0.63	0.75	0.46	0.01	0.01	0.01	61.2	1.5	5.3	1.4
11-2	193	1.012	20.4	1.02	0.78	0.62	0.01	0.06	0.01	79.0	1.8	7.4	1.7
2-5	197	1.010	6.7	0.56	0.51	0.17	0.01	0.03	0.01	88.8	2.2	6.5	1.5
7-8	254	1.010	10.0	0.73	0.63	0.70	0.02	0.04	0.01	79.2	2.8	6.2	1.4
8-8	2,623	1.006	100.7	8.02	4.55	3.73	0.14	0.28	0.07	82.1	3.1	6.2	1.5
Total	3,397		137.8	10.99	7.25	5.78	0.19	0.15	0.11				

TABLE 3—Balance of Water, Nitrogen and Chloride During Metabolism Period (Case 1)

	Intake			Output						Balance			Remarks
	Water, C c	Nitrogen, Gm	Chlorid, Gm	Water, C c			Nitrogen, Gm			Chlorid, Gm	Nitrogen, Gm	Chlorid, Gm	
				Urine	Feces	Total	Urine	Feces	Total				
July 7, 1920	7,185	10.69	16.60	7,032	86	7,118	9.88	1.12	10.70	15.89	0.21	16.10	Normal
July 8, 1920	6,705	10.52	15.52	6,467	86	6,493	8.49	1.12	9.61	15.64	0.21	15.85	Normal
July 9, 1920	2,865	10.76	15.52	1,942	40	1,982	8.31	0.49	8.80	12.51	0.07	12.58	Pituitrin
July 10, 1920	2,345	11.12	15.77	3,397	40	3,437	7.21	0.49	7.74	10.99	0.07	11.56	Pituitrin

ment, but dropped considerably on the second day Chlorids in the urine decreased on the first day and were lower on the second day The nitrogen balance was slightly positive in the period before treatment, with a slight retention on the first day and greater retention on the second day of treatment The chlorid balance was similar to the nitrogen except that the equilibrium was more nearly established in the period before treatment, and retention in the after period of treatment was more marked On the last day, the nitrogen and chlorid balances

TABLE 1—*Water Balance Before and After Administration of Pituitary Extract (Case 1) \**

	Hours of Collection	Water Intake, C c			Water Output, C c			Balance, C c
		In Fluid	In Food	Total	Urine	In Feces	Total	
Before treatment July 7, 1920	8-11	960	475		862			
	11-2	720	475		712			
	2-5	960			823			
	5-8	720	475		721			
	8-8	2,400			3,914	86		
	Total	5,760	1,425	7,185	7,032	86	7,118	+67
July 8, 1920	8-11	1,200	475		544			
	11-2	720	475		755			
	2-5	720			820			
	5-8	960	475		808			
	8-8	1,680			3,480	86		
	Total	5,280	1,425	6,705	6,407	86	6,493	+212
During treatment July 9, 1920	8-11	480	475		248			
	11-2	480	475		317			
	2-5	0			147			
	5-8	480	475		150			
	8-8	0			1,080	40		
	Total	1,440	1,425	2,865	1,942	40	1,982	+883
July 10, 1920	8-11	480	475		130			
	11-2	480	475		193			
	2-5	0			197			
	5-8	480	475		254			
	8-8	480			2,623	40		
	Total	1,920	1,425	3,345	3,397	40	3,437	-1,012

\* A specimen of blood was taken at 11 a m, July 8, at 7 45 a m, July 9, the patient was given 1 cc pituitary extract (pituirin "O", Parke, Davis & Co) subcutaneously, and at 11 a m the other specimen of blood was taken At 8 a m, July 10, 1 cc. of Squibb's pituirin was given (Tables 2, 3 and 10)

were not parallel with the water balance The variations in urine volume and specific gravity were marked The excretion of acids and ammonia was slightly lower after the administration of pituitary extract The percentage of ammonia nitrogen to total nitrogen was also a little lower on the last day

Referring to the daily totals, it may be noted, especially on the second day of pituitary extract administration, that there was a drop in the excretion of all the materials examined This accounts for the positive chlorid and nitrogen balance, and indicates a retention of all these substances

in the first period, from 101 to 420 cc during treatment, and from 165 to 941 cc in the final period. The urine output in the last two days gradually increased in each three-hour period as the effect of the pituitary extract was wearing off, until during the last twelve hours,

TABLE 4—*Water Balance in the First Metabolism Experiment (Case 2)*<sup>a</sup>

	Time of Collection	Fluid Intake, C c			Fluid Output, Urine, C c	Balance, C c
		Water	Food	Total		
Before Treatment Sept 1, 1920	8-11	800	529		287	
	11-2	400	529		396	
	2-5	200			700	
	5-8	600	531		557	
	8-8	1,600			2,584	
	Total	3,600	1,589	5,189	1,525	+664
Sept 2, 1920	8-11	800	530		705	
	11-2	800	530		730	
	2-5	370			185	
	5-8	400	530		580	
	8-8	1,800			2,780	
	Total	4,150	1,590	5,740	4,980	+760
During Treatment Sept 3, 1920	8-11	200	531		185	
	11-2	1,000	531		115	
	2-5	0			125	
	5-8	200	531		120	
	8-8	200			420	
	Total	1,600	1,593	3,193	915	+2,278
Sept 4, 1920	8-11	200	526		230	
	11-2	200	526		210	
	2-5	200			210	
	5-8	200	528		115	
	8-8	0			405	
	Total	800	1,580	2,380	1,200	+1,180
After Treatment Sept 5, 1920	8-11	200	510		165	
	11-2	200	510		175	
	2-5	0			195	
	5-8	400	512		405	
	8-8	2,400			3,505	
	Total	3,200	1,532	4,732	1,445	+287
Sept 6, 1920	8-11	400	510		660	
	11-2	1,400	510		485	
	2-5	800			125	
	5-8	200	512		625	
	8-8	2,050			3,765	
	Total	4,850	1,532	6,382	5,060	+422

<sup>a</sup> In the first experiment, blood was taken before breakfast at 8 30 a. m., September 3 and 4. September 3, at 7 30 a. m., 1 cc of pituitary extract (Parke, Davis & Co. pituitrin "S") was given, and blood was withdrawn at 8 40 a. m. The pituitrin was repeated at 8 15 p. m. September 4, at 8 45 a. m., the next specimen was taken. The pituitrin was repeated at 5 p. m. September 5 blood was taken before breakfast, at 8 45 a. m., and September 6 at 8 20 a. m. Symptoms of thirst began about 8 p. m., September 6 (Tables 5, 6 and 11).

when the excretion was higher than at any time during the period before treatment.

The positive balance of water in the normal period was considerably higher than in Case 1 and approximates the amount excreted daily through the lungs and the skin by a normal person. The marked

CASE 2<sup>18</sup>—Mr C H H, aged 39 years, came to the Clinic on Sept 10, 1920. He gave a history of having had diphtheria and scarlet fever at the age of 6 years, typhoid fever at 7, syphilitic infection with orchitis at 26, and an indefinite illness of gradual onset characterized by weakness, dark yellowish complexion, poor appetite and sleepiness at 32. A physician diagnosed syphilis and advised intensive treatment. Three months later the patient had a sudden onset of thirst and polyuria, he drank from 11 to 14 liters of water daily. About this time he commenced to notice decrease in libido and potentio which progressed to complete loss during the last two years. With the onset of polyuria, he also noticed loss of facial and axillary hair.

At the time of examination, the patient weighed 172 pounds (78 kg). The skin was dry, lifeless and sallow. The testicles were small and atrophic.

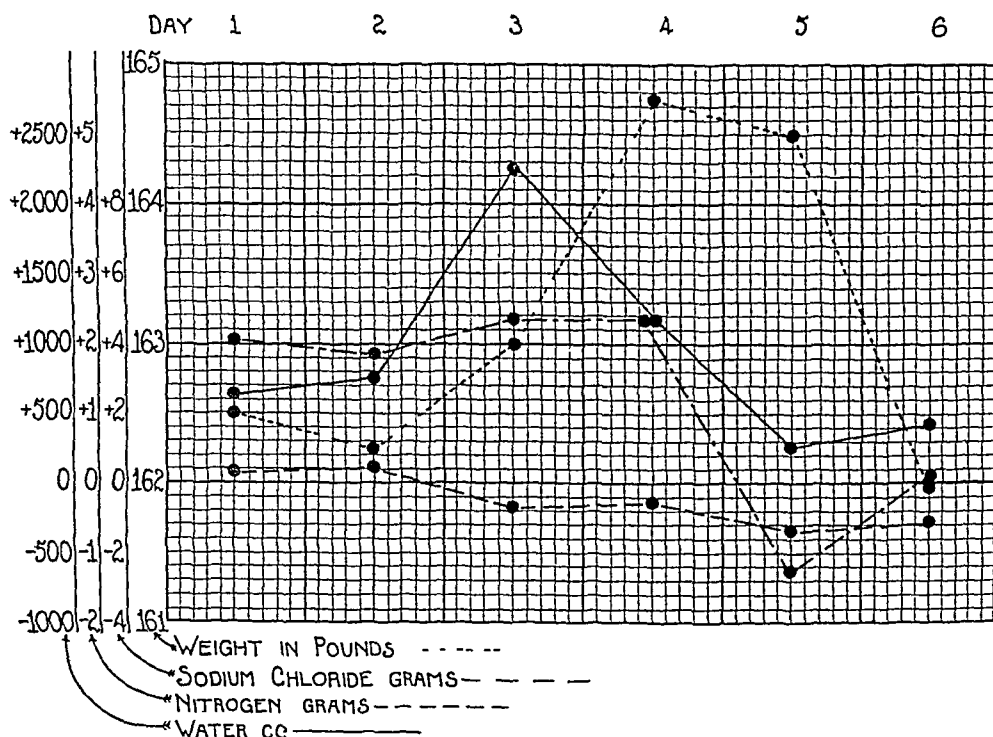


Fig 2 (Case 2) —Weight and balance of water, nitrogen and chlorids during first metabolism experiment

The basal metabolism varied from  $-31$  to  $-15$ . The spinal fluid revealed a positive Nonne reaction and 12 lymphocytes. Other laboratory tests were uniformly negative.

#### RESULTS OF OBSERVATIONS IN CASE 2

In Table 4 the water intake alone for each three hourly period is shown to vary from 200 to 800 cc before treatment, from 0 to 398 cc (omitting the one period from 11 to 2 on September 3, when 1,000 cc were taken) during treatment, and from 0 to 600 cc during the period after treatment. The urine output alone varied from 185 to 695 cc.

<sup>18</sup> McNeal, M.D. The Male Sexual Gland in the Prevention of Creatinuria, *Am J M Sc* **164** 222-227, 1922.

TABLE 6—Balance of Water, Nitrogen, and Chlorid in the First Metabolism Experiment (Case 2)

	Intake			Output			Balance			Weight, Pounds	Remarks
	Water, O c	Nitrogen, Gm	Chlorid, Gm	Water, O c	Nitrogen, Gm	Chlorid, Gm	Water, C c	Nitrogen, Gm	Chlorid, Gm		
Sept 1, 1920	5,180	8.42	9.80	4,325	8.27	7.70	+654	+0.15	+1.10	162.5	Normal
Sept 2, 1920	5,740	8.22	10.52	1,680	8.02	6.76	+740	+0.20	+3.76	162.25	Normal
Sept 3, 1920	3,193	7.78	8.93	915	8.11	4.27	+2,278	-0.36	+4.71	163.0	Pituitrin
Sept 4, 1920	2,380	7.92	10.35	1,200	8.20	5.61	+1,180	-0.28	+4.74	164.75	Pituitrin
Sept 5, 1920	4,732	8.61	9.36	1,445	9.27	11.86	+287	-0.66	-2.50	164.5	Normal
Sept 6, 1920	6,382	7.57	9.55	3,960	8.02	9.43	+122	-0.45	+0.12	162.0	Normal



TABLE 5—Urine Partition on the First Metabolism Experiment (Case 2)

Time	Volume, O c	Specific Gravity	Acidity, O c 0.1 Normal Acid	Sodium Chloride, Gm	Total Nitrogen, Gm	Urea Nitrogen, Gm	Ammonia Nitrogen, Gm	Creatinin Nitrogen, Gm	Uric Acid Nitrogen, Gm	Urea Nitrogen, Total per Cent	Ammonia Nitrogen, Total Nitrogen, per Cent	Creatinin Nitrogen, Total Nitrogen, per Cent	Uric Acid Nitrogen, Total Nitrogen, per Cent
Sept 1, 1920													
8-11	287	1.004	92.6	0.61	0.08	0.38	0.03	0.05	0.01	56.2	4.4	7.1	1.2
11-2	396	1.008	38.8	0.58	0.97	0.46	0.05	0.05	0.01	47.2	5.6	5.4	1.0
2-5	700	1.006	71.6	0.93	1.19	1.03	0.03	0.06	0.01	86.3	3.3	4.6	3.6
5-8	557	1.006	66.5	0.86	1.16	1.08	0.04	0.05	0.01	92.9	3.9	4.5	1.0
8-8	2,535	1.010	198.5	2.73	4.34	3.60	0.15	0.11	0.05	85.4	3.4	2.7	1.1
Total	4,525		398.0	5.70	8.24	6.55	0.31	0.32	0.09				
Sept 2, 1920													
8-11	705	1.005	33.1	0.99	0.95		0.02	0.06	0.01		2.6	6.7	1.3
11-2	730	1.007	35.9	1.25	0.95		0.03	0.06	0.01		3.0	6.2	1.4
2-5	135	1.019	32.5	0.43	0.76		0.01	0.05	0.01		0.7	7.1	0.3
5-8	580	1.006	65.5	0.66	1.05		0.05	0.07	0.01		4.4	6.2	0.9
8-8	2,780	1.009	176.5	3.43	4.30		0.16	0.27	0.01		3.7	6.3	1.7
Total	4,980		343.5	6.76	8.02		0.27	0.51	0.05				
Sept 3, 1920													
8-11	135	1.022	18.0	0.61	0.81	0.61	0.01	0.06	0.01	76.2	1.8	7.4	1.4
11-2	115	1.029	11.5	0.66	0.95	0.59	0.27	0.06	0.01	59.4	26.7	6.4	1.1
2-5	125	1.030	47.8	0.82	1.04	0.84	0.04	0.06	0.01	90.5	4.2	5.6	0.7
5-8	120	1.022	63.3	0.48	1.09	0.50	0.04	0.09	0.01	73.0	3.7	5.7	0.9
8-8	420	1.020	139.0	1.70	4.21	3.15	0.10	0.25	0.03	74.8	2.4	5.9	0.8
Total	915		268.1	4.27	8.13	5.49	0.46	0.49	0.07				
Sept 4, 1920													
8-11	230	1.023	17.2	0.96	1.31	1.17	0.02	0.07	0.02	89.3	1.5	5.6	1.6
11-2	210	1.020	54.9	0.74	1.14	1.02	0.04	0.07	0.02	88.9	3.8	5.7	1.3
2-5	240	1.022	89.5	0.76	1.09	0.90	0.03	0.06	0.01	82.0	3.7	5.2	1.1
5-8	115	1.037	65.5	0.61	0.89	0.83	0.03	0.06	0.02	93.0	3.7	6.8	1.7
8-8	405	1.019	128.5	2.54	3.77	3.18	0.07	0.27	0.06	84.3	1.9	7.2	1.5
Total	1,200		355.7	5.61	8.20	7.10	0.20	0.53	1.13				
Sept 5, 1920													
8-11	165	1.024	14.9	1.11	1.29	1.13	0.03	0.08	0.02	87.7	2.0	6.1	1.6
11-2	175	1.027	27.0	1.02	1.37	1.01	0.03	0.06	0.02	73.7	2.1	4.5	1.1
2-5	195	1.021	49.8	0.97	1.14	1.00	0.06	0.06	0.01	87.0	5.8	5.6	0.9
5-8	405	1.011	69.0	1.09	1.20	1.09	0.06	0.06	0.01	90.3	4.7	5.3	1.1
8-8	3,505	1.006	157.0	7.67	4.26	3.77	0.14	0.23	0.06	88.6	3.2	5.5	1.4
Total	4,445		317.7	11.86	9.26	8.00	0.32	0.49	0.12				
Sept 6, 1920													
8-11	660	1.004	20.9	1.22	0.95	0.73	0.03	0.06	0.01	75.8	3.6	6.5	1.4
11-2	485	1.007	46.6	0.86	0.99	0.70	0.05	0.06	0.01	79.9	5.5	5.8	1.1
2-5	425	1.009	56.2	0.74	0.98	0.82	0.06	0.06	0.01	84.0	5.8	5.9	1.4
5-8	625	1.007	68.0	0.84	1.05	0.80	0.05	0.05	0.01	76.6	4.8	4.6	0.9
8-8	3,765	1.004	217.0	5.77	4.05	3.25	0.11	0.25	0.07	93.3	2.7	6.1	1.7
Total	5,960		418.7	9.43	8.03	6.39	0.30	0.48	0.11				

relative decrease in the amount of plasma. The molecular concentration remained practically unchanged. There was slight increase in uric acid and creatinin.

In Case 2, practically no change in relative plasma volume occurred during the first observation. Molecular concentration was increased on the first day of treatment, but dropped on the second day, was still lower on the first day following cessation of treatment, but rose to its highest level on the succeeding day. The total amount of nitrogen and sodium chlorid decreased during the period of treatment and increased again in the period after treatment. No distinct change was seen in the other elements.

TABLE 7—*Blood Analysis Before and During Administration of Pituitary Extract (Case 1)*




July 1920	Hematocrit Plasma, per Cent		Plasma, Mg for Each 100 C c		Whole Blood, Mg for Each 100 C c				Remarks
			Total Nitrogen	Sodium Chlorid	Urea Nitrogen	Uric Acid	Creatinin	Sugar	
8	62	0.528		600	11	5.6	1.2	133	Normal Pituitrin
9	57	0.530		573	5	6.6	1.5	93	

TABLE 8—*Blood Analysis (Case 2), First Observation*

September, 1920	Hematocrit Plasma, per Cent		Plasma for Each 100 C c		Whole Blood, Mg for Each 100 C c					Remarks
			Total Nitrogen, Gm	Sodium Chlorid, Mg	Non-protein Nitrogen	Urea Nitrogen	Sugar	Uric Acid	Creatinin	
1	67	0.515	1.171	648	29.8	14.9	128	2.7	1.9	Normal
2	70	0.530	1.142	653	26.5	14.9	108			Normal
3	69	0.542	1.082	640	26.6	16.2	144			Pituitrin
4	72	0.531	1.060	623	24.8	14.8	108			Pituitrin
5	71	0.522	1.099	633	28.1	14.8	108			Normal
6	69	0.546	1.129	648	27.0	13.3	112			Normal

Second Observation

1921	Hematocrit Plasma, per Cent		Plasma for Each 100 C c			Whole Blood, Mg for Each 100 C c					Remarks
			Carbon Dioxid, Volume, per Cent	Total Nitrogen, Gm	Sodium Chlorid, Mg	Non-protein Nitrogen	Urea Nitrogen	Sugar	Uric Acid	Creatinin	
Feb 25	60	0.548		1.260	570	28.3	12.5	58	2.3	1.4	Normal
26	60	0.528	58	1.287		31.9	17.6	78	2.1	1.7	Normal
27	61	0.530	68		580	28.6	13.2	71	2.4	1.5	Pituitrin
28	69	0.491	66	1.182	590	28.3	15.0	112	2.2	1.5	Pituitrin
Mar 1	68	0.520	68	1.070	580	32.0	16.7		1.9	1.5	Normal
2	68	0.537	68	1.120	595	29.6	15.7		2.3	1.5	Normal

During the second period of observation of this case, there was a rather marked increase in the relative plasma volume and decrease in the molecular concentration, with a slight decrease in the total nitrogen of the plasma on the second day of treatment. These changes were preceded on the previous day by a rise in the carbon dioxide combining power of the plasma. In the period after treatment, the molecular concentration returned to its previous level, but the relative plasma volume and carbon dioxide combining power remained elevated. The other elements showed no noteworthy changes.

CASE 3—A nervous, poorly developed woman, aged 37 years, came to the Clinic on Feb 24, 1921. She had had typhoid fever at 17, and intense thirst,

increase in retention of water after the first dose of pituitary extract corresponded to the marked drop in urine output and confirmed the observation made in Case 1. The simultaneous increase in weight (Table 6) in this case, as well as the increased excretion in the final period, indicated a retention of the water in the blood or tissues. The excretion of nitrogen in urine showed no change under administration of pituitary extract, but increased in the first day of the period after treatment. A distinct drop in the chlorids in the urine was noted, under the effects of the drug, with an increased excretion in the period after treatment. The nitrogen balance throughout was negative and showed no appreciable change as in Case 1. The chlorid balance showed a slight retention in the period of treatment and a negative balance in the period after treatment. In this final period, the chlorid balance ran parallel to the water. In the urine, the marked variations in volume and specific gravity were again noted. The excretion of acid and ammonia did not definitely change, and no other characteristic variation in the total or percentage of excretion of the other elements in the urine was noted<sup>19</sup>.

During a second observation, the urine was collected as usual, but examination was made of the twenty-four hour specimen only. The water intake was determined for each twenty-four period.

In the period before treatment the urinary output in three hourly periods varied from 375 to 1140 c c, in the period of treatment from 70 (average of specimen from 8 p m, February 27, to 8 a m, February 28) to 560 c c, and in the period after treatment, from 175 to 990 c c.

Equilibrium was fairly well established in the balance of water, nitrogen and chlorid, by the second day of the period before treatment. The positive water balance did not change appreciably during the period of treatment, but the gain in weight in this period and the large negative water balance and drop in weight in the period after treatment were significant. No definite conclusions could be drawn from the balance of nitrogen and chlorids.

The marked variations in urine volume, specific gravity and molecular concentration, were again seen. No definite variations occurred in the total or percentage excretions of the other elements determined.

#### EFFECTS OF PITUITARY EXTRACT ON COMPOSITION AND VOLUME OF BLOOD IN FOUR CASES OF DIABETES INSIPIDUS

In Case 1, a decrease in the level sodium chlorid, urea and sugar in the blood was noted after pituitary extract had been administered. There was a

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<sup>19</sup> The collection of feces in this case was unsatisfactory and the results are omitted.

For two years, thirst, polyuria and weakness had gradually developed. She gave a long psychoneurotic-like history that suggested a diagnosis of migraine and petit mal. The urine output and thirst had been excessive for six weeks.

At the time of examination the patient weighed 104 pounds (47.17 kg). Examination of the heart revealed chronic mitral endocarditis (stenosis and regurgitation), otherwise physical and laboratory examinations were negative.

There was no change in the relative plasma volume or total nitrogen content after administration of pituitary extract. However, there was a marked decrease in the molecular concentration and in sodium chloride content. The other elements examined remained unchanged.

#### COMMENT

In viewing these results as a group, it may be noted that all the elements of the blood in these cases are within normal limits, both before and after the administration of pituitary extract.

Table 11 shows that the molecular concentration, total nitrogen and sodium chloride are usually decreased, and that relative plasma volume usually shows an increase after administration of pituitary extract. These changes seem to indicate a dilution of the blood when the excessive elimination of fluid by the kidneys is checked by the administration of pituitary extract, and contrasts with the absence of such changes in normal persons under the influence of pituitary extract. However, the changes are neither constant nor marked, and too much importance should not be attached to them.

#### EFFECT OF DRINKING WATER AFTER ADMINISTRATION OF PITUITARY EXTRACT


In Case 1, pituitary extract was administered, and the patient was urged to drink water in the amounts to which he had previously become accustomed. In a few hours he began to complain of headache, dizziness, nausea, malaise and weakness. Perspiration was free. There was evidence of edema at the ankles and in the loose tissues around the eyes. The water intake was at once discontinued, and the edema and symptoms gradually disappeared. The patient later repeated the experiment, but did not drink as much as before. In seven to eight hours, there was a recurrence of the symptoms, but without edema. The blood examination before the experiment began and after the development of symptoms (Table 12) showed a marked increase in relative plasma volume, but no accompanying change in the molecular concentration, total nitrogen, sodium chloride or urea content of the blood.

In view of this water intoxication, the routine water test of renal function was given in Case 2. At 8 a. m., the patient drank 2,000 cc of water within thirty minutes on a fasting stomach. Urine was collected and measured, and the specific gravity determined every half hour for four hours (Table 13). No pituitary extract was given before or during this test. After the ingestion of the water, the

polyuria and weakness, headaches, pain in neck, and nervousness began suddenly in March, 1920


She was somewhat anemic, but the physical examination was essentially negative. Her husband had syphilis with definite evidence of involvement of the central nervous system. In view of this, a lumbar puncture was made, revealing a positive Nonne reaction and 13 lymphocytes for each cubic centimeter. Wassermann reactions and the neurologic examination were negative.

TABLE 9—*Blood Analysis (Case 3)* \*

July, 1920	Hematocrit Plasma, per Cent		Plasma for Each 100 C c		Whole Blood, Mg for Each 100 C c			Remarks
			Total Nitrogen, Gm	Sodium Chlorid, Mg	Urea Nitrogen	Uric Acid	Creatinin	
15	61	0.522	1.058	629	5.0	2.4	1.3	Normal
16	55	0.549	1.163	640	5.8	2.4	1.3	Normal
17	67	0.549	0.940	607	6.6	2.4	1.3	Pituitrin
18	67	0.513	0.970	597	6.1	2.3	1.3	Pituitrin

\* Blood was taken before breakfast at 8:30 a. m. on July 15 and 16 and at 8:15 a. m. on July 17 and 18. Pituitary extract (Parke, Davis & Co., pituitrin "0") was given in 1 c.c. doses at 6 a. m. and 8 p. m. on July 17 and at 6 a. m. on July 18.

TABLE 10—*Blood Analysis (Case 4)* \*

August, 1920	Hematocrit Plasma, per Cent		Plasma for Each 100 C c		Whole Blood, Mg for Each 100 C c			Remarks
			Total Nitrogen, Gm	Sodium Chlorid, Mg	Non-protein Nitrogen	Urea Nitrogen	Sugar	
3	66	0.544	0.980	588	28		123	Normal
4	65	0.530	0.927	589	23	5.0	114	Normal
5	65	0.501	0.905	565	27	6.3	114	Pituitrin
6	66	0.514	1.022	560	28	5.7	114	Pituitrin
7	61	0.512	0.964	576	28	6.5		Pituitrin

\* Blood was taken before breakfast at 8:30 a. m. on every day of the experiment, August 3 to 7 inclusive. Pituitary extract (Parke, Davis & Co., pituitrin "0") was given in 1 c.c. doses at 6 a. m. August 5, 6 and 7.

TABLE 11—*Summary of Blood Changes in Four Cases of Diabetes Insipidus During Treatment with Pituitary Extract*

Case	Relative Plasma Volume by Hematocrit	Molecular Concentration	Total Nitrogen	Sodium Chlorid
Case 1				
1	Decrease	No change		Decrease
2	Increase	No change	Decrease	Decrease
Case 2				
1	No change	Decrease	Decrease	Decrease
2	Increase	Decrease	Decrease	No change
Case 3	Increase	Decrease	Decrease	Decrease
Case 4	No change	Decrease	No change	Decrease

The changes in the blood in this case after the administration of pituitary extract were the most distinct of any studied. The relative plasma volume was increased, and molecular concentration decreased, both indicating a dilution. The plasma content of total nitrogen and sodium chlorid was decreased after the administration of pituitary extract. No noteworthy changes in the other elements occurred.

CASE 4—A woman, aged 28 years, came to the Clinic on July 5, 1920. She had had frequent attacks of tonsillitis and influenza in 1918 and 1919.

the effect of pituitary extract had worn off. In no instance was there diarrhea after the administration of the drug, and analysis of feces in one case failed to reveal increased elimination of water by bowel.

Great care must be exercised in interpreting changes in the balance calculated from the excretion of nitrogen, chlorids and other elements in the urine. However, there is some evidence of a decreased total excretion of nitrogen, chlorids, acids and ammonia with increasing elimination of these substances again as the effects of the drug disappear. These changes are of minor importance and may readily be due to the outstanding variations in water exchange.

In studying the blood it was found that there was a slight relative increase of plasma volume, and a relative decrease in total nitrogen molecular concentration and sodium chlorid of the plasma after the administration of pituitary extract. These were not constant or marked. However, they suggest a dilution of the blood which may also explain the phenomena of decreased excretion of nitrogen and chlorids in urine.

Changes in the water content of the tissues<sup>20</sup> must not be overlooked, for in the one case in which toxic signs developed from over-ingestion of water after administration of pituitary extract, definite edema was present. Determinations of blood volume<sup>21</sup> have not given constant results. Blood dilution constitutes an adequate explanation of the relief from the thirst, although a more complicated mechanism than simple dilution is undoubtedly involved. Again, dilution of the blood is one of the most effective methods of increasing urinary secretion in a normal person, but this increase does not occur when pituitary extract has been administered to patients with diabetes insipidus. At least, it is not constant, and some other explanation must be sought. The increase in weight of the patients noted during the experiments, the decrease after, and the changes in water balance prove the retention of water. The occurrence of edema in the toxic patients, and the minor changes in the blood indicate involvement of the body tissues. This may mean a raised renal threshold for water, as well as a change in the relative ease with which water passes from the blood to the tissues as compared with the ease with which it passes from the blood through the kidney. In other words, it is not known whether pituitary extract affects the renal tissue primarily, the water threshold being raised and the retained water distributed according to present known laws, or whether all the body tissues are affected by this drug in a more or less similar manner.


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21 Weir, J. F., Larson, E. E., and Rowntree, L. G. Studies in Diabetes Insipidus, Water Balance, and Water Intoxication. Study I, *Arch. Int. Med.* 29: 306-330 (May) 1922.

patient noted chilliness and abdominal distress. After from three-fourths of an hour to one hour, he suffered general distress. Then his skin became moist, and he perspired freely. He said, "This is the first real sweat I have had for a long time." Later he became nervous and depressed, and lost "pep." He exhibited no tremor objectively, but experienced a shaking sensation in his limbs. A slight headache developed, his mouth became moist, and he lost thirst throughout the day. During the four hours following the intake of the water, the urine output amounted to only one-half the intake. This suggests, in comparison with normal reactions, an impairment of renal function.

TABLE 12—*Blood During Intoxication with Water After Administration of Pituitrin (Case 1) \**

July, 1920	Hemat- ocrit Plasma, per Cent		Plasma for Each 100 C c		Urea Nitrogen in Whole Blood, Mg for Each 100 C c	Remarks
			Total Nitrogen, Gm	Sodium Chlorid, Mg		
19	58	0.527	1.096	555	14	Before pituitrin
20	71	0.528	1.000	551	14	During symptoms after pituitrin

\* Blood was taken at 11 a. m. on July 19. At 11 a. m., July 20, 1 c.c. pituitary extract (Parke, Davis & Co., pituitrin "O") was given and the patient ingested 3,120 c.c. of water up to 8 p. m. At 10 p. m. the second specimen of blood was taken.

TABLE 13—*Result of Routine Water Test of Renal Function (Case 2)*

Time	Volume, C c	Specific Gravity
8 30 to 9 00	400	1.005
9 00 to 9 30	320	1.004
9 30 to 10 00	100	1.004
10 00 to 10 30	0	
10 30 to 11 00	200	1.004
11 00 to 11 30	0	
11 30 to 12 00	65	1.007
12 00 m to 8 00 a m	3,500	1.006
Total	4,495	

## DISCUSSION

The study of the urine and metabolism of two patients with diabetes insipidus disclosed a marked decrease in volume, with a corresponding increase in the specific gravity and molecular concentration (one patient) of the urine after the administration of pituitary extract. With this decrease in volume, there was a disappearance of the distressing clinical symptom of thirst. The weight during two experiments on the same patient was definitely increased, while the normally slightly positive water balance increased markedly. The urine in the period after treatment was increased above that of the period before treatment, indicating retention and confirming the patient's statement that there was always a temporarily increased amount of urine after

# GASTROSCOPY IN THIRTY CASES OF GASTRIC NEOPLASM \*

R SCHINDLER

MUNICH, GERMANY

Among all the known pathologico-anatomic forms of gastric tumor, carcinoma alone has been susceptible of diagnosis until the present time. In rare cases a tumor recognized by roentgen-ray examination has proved at operation to be a benign polyp. Still rarer has been the diagnosis of sarcoma from vomited tumor fragments.

Only gastroscopy renders it possible to recognize the different forms of tumor. Through it we shall probably be forced to revise our ideas regarding the symptomatology of new growths. Much investigation is still necessary to reach determinate results.

My observations were made in 400 gastroscopic examinations performed in the Munich-Schwabing hospital. They were made with a gastroscope of my own modification. Examination with this instrument if expertly used is almost without discomfort to the patient. The technic is not easy, and much practice is necessary to apply it safely and painlessly, but the diagnostic results are so excellent that the investigator with some knowledge of endoscopy will not be deterred by this difficulty. In contradistinction to round ulcer, which, if situated at the pylorus, is difficult of examination, all neoplasms of the stomach offer a fruitful field of observation.

## BENIGN TUMORS

Only such tumors as are situated on the inner aspect of the stomach can be recognized by the gastroscope. These include myomas, fibromyomas, mucous polyps (solitary or multiple) and papillomas. Lymphangiomas and cavernous angionas occur but are rare.

*A Fibromyoma*—Fibromyomas are usually small and situated near the cardia. I have diagnosed two cases with the gastroscope.

CASE 1—T. S., a clerk, aged 60, had lost weight for a year on account of undernourishment. He had pain in the stomach after meals. He had lost his appetite. He did not vomit. There were no objective signs. His tongue was coated. He had pulmonary tuberculosis. Examination revealed free hydrochloric acid, 0, total acidity, 4, lactic acid, 0. Microscopic examination revealed leukocytes, yeasts, and sarcinae. The roentgen-ray examination was negative. Bowel movements were variable, he was usually constipated, occasionally he had colic.

Gastroscopy revealed low stomach, pyloric action normal, mucous membrane in region of antrum elevated, rugged and uneven. On the cardiac sphincter there was a tumor the size of a cherry, pendant into the fornix, and

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\* Translated by Lynn Rogers, Chicago



## CONCLUSIONS

1 Observations following the administration of pituitary extract to patients with diabetes insipidus confirm the previously recorded findings of a marked decrease in urinary output with corresponding increase in specific gravity and molecular concentration coincident with a temporary disappearance of the distressing clinical symptoms

2 The simultaneous increase in weight and increase of positive water balance and the increased elimination after the effects of the drug have worn off indicate a retention of water in the blood or tissues

3 Changes in the excretion of nitrogen, chlorids, acids and ammonia may be due to direct action of the pituitary extract on the kidney or may be secondary to the changes in water excretion

4 The retention of water in the blood and tissues overshadows any possible retention of nitrogen and chlorin

5 The blood of these patients presents slight and somewhat inconstant evidences of dilution The occurrence of edema in one case subsequent to forcing water proves that some, at least, of the retained fluid is distributed to the tissues of the body

6 Dilution of the blood and an increased tissue content of water produced an increased flow of saliva with the cessation of thirst

7 The dilution of the blood does not appear sufficient to stimulate the kidneys of patients with diabetes insipidus who have received pituitary extract However, this dilution is neither marked nor constant, and some change in the renal permeability is undoubtedly induced The extent to which the tissues are affected is as yet unknown

8 Forcing water to patients with diabetes insipidus subsequent to administration of pituitary extract leads to the development of toxic manifestations

9 In diabetes insipidus, pituitary extract raises the secretion threshold of the kidney for many substances, but especially for water It is not yet clear to what extent it affects the relative ease with which water leaves the vascular system to enter the tissues or to be excreted by the kidney

repeated revealed the same condition. The mucous membrane everywhere, and especially in the pyloric region, presented nodular and finger-shaped excrescences. On the anterior wall there was a hemispherical tumor entirely covered with whitish mucus (most probably an adenomatous polyp). On the posterior wall of the fundus there was a gastro-enterostomy opening, functioning rhythmically and energetically. The pylorus was extant and functioning normally.

Diagnosis Polyposis ventriculi

In this case also it is not entirely clear whether the discomfort was caused by the gastro-enterostomy or the polyp. The latter seemed probable, as the gastro-enterostomy functioned normally.

Gastroscopic differential diagnosis between real polyps and the inflammatory growths of gastritis chronica polyposa is not difficult. Real polyps protrude from smooth shiny normal membrane and are themselves covered with smooth orange-colored mucosa. Pseudopolyps of chronic gastritis protrude from a dull, elevated, puffy mucosa and have a bluish translucence.

*C Papilloma*—I have not had an opportunity to observe this rare benign tumor. Through the gastroscope it would be indistinguishable from carcinoma papillosum, also rare. The therapy would therefore necessarily be surgical. The picture presented would resemble the cystoscopic one of papilloma.

#### MALIGNANT TUMORS

Among metastatic tumors, melanotic sarcomas, easily recognized by their black color, are most frequent. Metastatic carcinomas, which are apt to form multiple nodular and ulcerated metastases, are rare. Sarcomas of various kinds occur in the stomach in addition to the frequent carcinomas.

*A Sarcoma*—The ordinary nodular round-celled sarcomas are not easily distinguishable from similar carcinomas, whereas the diffuse lymphosarcomas present a characteristic picture.

CASE 5—C N,<sup>1</sup> a housekeeper, aged 60, had pain in the stomach. She had lost weight and appetite. Examination revealed no free hydrochloric acid, a total acidity of 5, no rennin, or pepsin, and no lactic acid. Microscopic examination revealed leukocytes, erythrocytes, bacteria and sarcinae. Roentgen-ray examination revealed stasis in the duodenum.

First gastroscopy. The mucosa of the lesser curvature was elevated, there were areas of submucous hemorrhage which in one place had broken through the mucous membrane. Second gastroscopy. This was performed four months later. The whole membrane was greatly changed, showing everywhere large areas of diffuse hemorrhage. The greater curvature of the fundus presented rigid streaks and bands showing a nodular surface. If it had not been for the greatly advanced changes in the mucosa, the diagnosis might have been carcinoma. The diagnosis was gastritis proliferans of an unusual type. The patient declined operation, and four months later died of perforative peritonitis. Necropsy revealed diffuse lymphosarcoma of the stomach.

<sup>1</sup> This case was reported in great detail in Klin Wchnschr 42 2086, 1922

covered with smooth bright red membrane without ulceration Gastroscopic Diagnosis Chronic hypertrophic gastritis, small pea-sized tumor of the cardia, myoma or carcinoma

Although the tumor gave the impression of being benign, gastroscopy was repeated after two and four weeks Through careful dieting the hypertrophic gastritis was nearly healed, but the tumor was entirely unchanged On account of its location at the cardia, the diagnosis of myoma, specifically fibromyoma, was made

CASE 2—In this case also the tumor was incidental

M G, a scrubwoman, aged 45, for three years had had pain in the stomach some time after meals, relieved by eating There had been vomiting of blood and tarry stools The condition was diagnosed as being in all probability duodenal ulcer

Gastroscopy The whole stomach was well illuminated Pyloric action was normal There was no ulcer The mucosa was very pale On the anterior wall there was an irregularly bordered area, gray-green and thinned out, the mucous membrane showing no red tint Somewhat higher but still below the cardia, there was a small half spherical tumor protruding into the lumen and covered with pale mucous membrane Gastroscopic diagnosis Anemia, circumscribed atrophic gastritis of the anterior wall and subcardial fibromyoma

At the second gastroscopic examination the anemia was improved, the other conditions were unchanged

In both cases I consider the fibroma incidental and believe that its association with unusual gastric changes is fortuitous and that none of the subjective symptoms have any connection with the tumor

*B Mucous polyp*—Mucous polyp occurs either solitary or multiple (polyposis ventriculi) We distinguish simple mucous polyp, cystic and papillary adenoma

CASE 3—P H, a day laborer, aged 45, had dysentery during the war Since then he had had stomach pains unrelated to meals He had attacks of colic There were objective signs A test breakfast revealed free hydrochloric acid, 0, total acidity, 8, lactic acid, 0, absence of pepsin The microscopic examination was negative There was no blood in the stools Diagnosis Achylia gastrica and gastrogenic diarrhea following dysentery

Gastroscopy There were surprising findings in the antrum A transparent reddish fold contracted and revealed the sphincter of the antrum which after the manner of the pylorus closed tightly with the formation of thick, elevated folds and creases so that the cavity of the antrum became entirely shut off from the gastric cavity When the folds of the sphincter slowly relaxed they revealed a small irregular tumor between them, on the posterior wall

The cavity of the antrum was now exposed and a moderately broad expanse of tumor was perceptible on the posterior wall The normal pylorus became visible beyond

Diagnosis Polyp of the posterior wall of the antrum The polyp could also be demonstrated with the fluoroscope

In reporting this case I have concluded that the gastric pains are to be explained by the presence of the polyp, which is irritant to the pylorus, producing spasm This patient was examined twice

CASE 4—W D, a housekeeper, aged 31, thirteen years previously had had an operation for alleged ulcer On presentation she had pain in the stomach and vomiting There was no hydrochloric acid or pepsin Gastroscopy twice

The base of the ulcer may be vivid yellow or gray-red, like the surrounding mucosa, but much oftener it presents all the appearances of necrosis with marked variations of brown, violet, red, yellow, white and especially green. The green color of necrotic tissues as seen through the gastroscope is particularly characteristic. The mucosa in the region of the tumor occasionally shows small secondary ulcers. Otherwise it gives the picture either of chronic mucous catarrh with petechial injection and stringy and weblike deposits of tenacious mucus, or one sees on the apparently normal mucosa, various large atrophic gray-green islands, the frank picture of an atrophic gastritis. Rarely the pallid mucosa is dotted with petechial hemorrhages.

Scirrhus infiltration of the entire stomach wall produces the so-called "canteen stomach," a diminished tube with boardlike walls. As it cannot be inflated, gastrosopy is impossible. The differential diagnosis of certain terminal forms of hypertrophic gastritis can be made only postmortem.

The following is a brief history and description of the gastroscopic findings in twenty-five cases of carcinoma which I have examined. In eleven patients the lesion was at the pylorus, in seven on the lesser curvature, in six on the fundus and in one in the bowel immediately below the opening of a gastro-enterostomy.

#### CARCINOMA OF THE PYLORUS

CASE 6 —A S, a servant, aged 27, had a "weak stomach." The symptoms had been aggravated during the last three weeks. There were stomach pain, vomiting, extreme cachexia and anemia. Hemoglobin was 19 per cent, there were 1,300,000 erythrocytes. Emptying of the stomach was delayed. A test breakfast revealed free hydrochloric acid 10, total acidity 20. Fluoroscopic examination revealed an anatomic obstruction to the emptying of the stomach. Carcinoma was suspected.

Gastrosopy. The mucosa of the fundus was almost white. In the dependant portion there was coffee ground fluid. Before the pylorus could be examined the lamp burned out, and another was not available. Gastroscopic diagnosis. Probably carcinoma. The patient died in eight days. Necropsy revealed a large ulcerated carcinoma of the pylorus. Could gastroscopy have been continued, the large tumor could not have escaped the eye.

CASE 7 —J K, a factory worker, aged 42, had lost weight—four kilograms in four months—and had gastric pain after meals and a poor appetite. Examination showed retarded emptying of the stomach. The gastric juice contained no free hydrochloric acid, it contained lactic acid and blood. The stool contained blood. There was no palpable tumor. Radioscopic examination revealed probably an old ulcer with surrounding hyperplasia. Clinical Diagnosis. suspected carcinoma.

Gastrosopy. The antrum was only partly visible, a broad rigid elevation of the posterior wall intervened obscuring the light. Only a part of the pylorus was visible. It was rigid and without motility. There was no ulceration.

A biopsy was made. Operation revealed carcinoma of the pylorus and greater curvature, which were totally resected.

It is obvious that diagnosis of this case could have been possible only through the gastroscope

*B Carcinoma*—It is well known that gastric carcinoma is frequent Surgery is its only chance for cure The probability of successful radical extirpation is not bad if performed in time Many patients first show subjective symptoms when the tumor has become inoperable There is, however, a large percentage of patients in whom a diagnosis could be made much earlier than is the rule at present

I have formulated this rule When a person over 35 years of age suffers from gastric disturbances which do not disappear after internal treatment of from four to six weeks or when such a person shows an inexplicable loss of weight, he or she should undergo gastroscopy I vigorously support this opinion

Carcinoma presents a different gastroscopic picture in each case One finds rigid infiltration of the wall, small shallow ulcerations and round cup-shaped tumors which often show crater-like ulcerations (This is the most common form) There are also solid, slightly ulcerated tumors and papillomatous tumors

The picture varies greatly according to location of the tumor Often parts of tumors, frequently most important parts, remain hidden because of intervening portions of the normal stomach Ulcer particularly is sometimes hard to discern At times only a minute part of a large tumor is visible On account of optical distortion, it is hard at times to judge the exact size of the tumor

The colors of carcinomas are brilliant in the gastroscope—much brighter than in a postmortem preparation

In scirrhus infiltration of the stomach wall, the latter takes on an oddly rigid appearance and a grayish white color in sharp contrast to the normal orange hue

Solid tumors may be covered with apparently normal mucous membrane, protude far into the lumen of the stomach and present only a small ulcer at their summits, or they may expand into a hemispherical form, become brownish purple and throw strong shadows on the pale gastric wall

In one case there were white nodules probably covered with mucus It is noteworthy that in the frequent cup-shaped tumors the wall projects, usually dark red, from the much lighter colored normal mucosa Papillomatous cauliflower tumors are grayish red

The cancerous ulcer has an irregular eaten-out border Its borders are usually, not always, elevated, wall-shaped Its differential diagnosis from benign ulcer is usually easy, but at times difficult and occasionally impossible Often the pathologic diagnosis can be made only with the microscope

It is noteworthy that in this case gastroscopy proved of more value than radioscopy

CASE 11—Q B, aged 54, during the past year had lost weight and had had pain in the stomach. Radioscopy revealed a defect of the antrum and carcinoma.

First Gastroscopy. Around the funnel of the antrum there was a small abrupt circular tumor wall. The funnel showed red ulceration. Gastroscopic Diagnosis. Circular carcinoma of the pylorus.

The patient refused operation as his condition began to improve.

Second Gastroscopy. The same tumor was present, but the wall was now higher and more rounded. There was much funnel-shaped ulceration.

A biopsy was made. Operation revealed an ulcerated carcinoma of the antrum, the size of a saucer. It was completely resected.

Gastroscopy had therefore clearly shown the enlargement of the tumor notwithstanding the subjective improvement.

CASE 12—O N, a portress, aged 63, two months before had had nausea and had vomited. There was a large palpable tumor in the epigastrium. Radioscopy revealed carcinoma and almost complete stenosis.

Gastroscopy (repeated once). A large elevated, crater-like, ulcerated tumor was found in the pyloric region. The remaining mucosa was pallid. Gastroscopic Diagnosis. Carcinoma of the pylorus. Operation was refused. Necropsy revealed adenocarcinoma of the pylorus.

CASE 13—M R, a janitress, aged 56, for the past year had lost weight, had had pain in the stomach and had vomited. There was a tumor in the left umbilical region, there was normal emptying of the stomach. There was no free hydrochloric, or lactic acid or blood in the gastric juice. There was no blood in the stool. Radioscopy revealed a strikingly constant defect in the antrum. Carcinoma was suspected.

Gastroscopy. In the greater curvature there was an elevated tumor with raised margin and dish-shaped ulceration. The ulceration was dirty green-gray. The tumor projected into the antrum and covered the pylorus. The mucosa of the fundus showed gray-green atrophic areas traversed by fine vessels. Gastroscopic Diagnosis. Large extensively ulcerated carcinoma of the antrum and greater curvature. Biopsy was performed. Operation confirmed the gastroscopic findings. A large tumor was completely resected.

CASE 14—B G, a cook, aged 47, had had pain in the stomach for two years. In spite of radioscopic examination, her physician made a diagnosis of gastritis. Finally there was coffee-ground vomiting. There was a palpable tumor. Radioscopic diagnosis was carcinoma of the pylorus.

Gastroscopy. On the pyloric portion of the anterior wall there was a rough nodular ulcerated tumor covered with yellow secretion. The mucosa of the lesser curvature was markedly indented. Gastroscopic Diagnosis. Carcinoma of the pylorus with extension to the anterior wall and lesser curvature.

Necropsy revealed medullary carcinoma of the pyloric region with extension to the lesser curvature and anterior stomach wall.

CASE 15—J S, a machinist, aged 60, for the past five months had been treated for gastric catarrh. There had been loss of weight and vomiting of blood. Emptying of the stomach was delayed. There was no free hydrochloric acid, lactic acid was present. Microscopic examination revealed leukocytes, fat droplets, sarcinae, yeasts and lactic acid bacilli. There was an enormous tumor.

Gastroscopy. The fundus contained blackish fluid. In the antrum behind a rigid fold were granulation-like reddish ulcerated growths. There was a blackish brown coating. Gastroscopic Diagnosis. Carcinoma of the pyloric region.

It is as yet unknown whether complete rigidity of the pylorus means a pathologic process in every case. In conjunction with a rigid elevation of the posterior wall, such a finding established the diagnosis of carcinoma. As a beginner, I did not venture to make it, as I had never seen a tumor through the gastroscope.

In all of the following cases, definite diagnosis was made with the gastroscope.

CASE 8—A K, aged 64, had lost weight and had pain in the stomach, anemia and palpable tumor. Examination revealed no free hydrochloric acid, lactic acid and blood were present. Radioscopic examination revealed carcinoma of the pylorus.

Gastroscopy. Instead of the pylorus there was a deep crater-like depression, the surface was ulcerated, greenish black and dotted with minute hemorrhages. The ulceration was irregularly bordered by the mucosa of the anterior wall, which formed an elevated edge. Toward the normal anterior wall were mushroom vegetations. On the normal mucosa of the front wall toward the greater curvature was a sharply defined hour-glass shaped ulcer. The posterior wall of the tumor was overlaid with a nodular rigid fold of the posterior stomach wall. Stringy and coffee-ground greenish-brown deposits lay on the neighboring mucosa.

Gastroscopic Diagnosis. Crater-like ulcerated carcinoma of the pylorus involving the anterior and posterior walls of the stomach. At necropsy an ulcerated carcinoma was found involving the whole pyloric canal, extending to the fundus and mesogastrium.

I have described the condition minutely in order to give some conception of the color and plastic details. It would be impossible for the best artist to reproduce the exact coloring.

CASE 9—M H, a day laborer, aged 62, for three months had lost weight, there had been pain in the stomach, vomiting and anorexia. Emptying of the stomach was greatly delayed. There were free hydrochloric acid, sarcinae and bacteria. Radioscopic examination revealed marked infiltration of the lesser curvature. Clinical diagnosis. Frank carcinoma.

Gastroscopy (with Elsner's instrument). The pylorus was shut out from view by the marked protrusion of the lesser curvature. On the anterior wall of the antrum a reddish, ulcerated mass of tissue projected into the lumen. Gastroscopic diagnosis. Carcinoma of the pyloric region.

Although no necropsy was performed, I cite this case to show that at times only a small part of an unquestionably large tumor is visible.

CASE 10—H W, a glassblower, had lost weight and had had stomach pain during the past three months. He had had jaundice during the past twenty-eight days. He had large tumor of the liver. The stools were gray. The gastric juice contained no blood or free hydrochloric acid. Radioscopy. The stomach was somewhat enlarged. There was marked peristalsis and displacement to the left. Emptying of the stomach was somewhat delayed. There was duodenal stasis probably caused by some external enlargement or pressure.

Gastroscopy. At the end of the lesser curvature there was a large tumor, with a dark central depression and large gray, greenish and whitish ulcerations. The margin was dark red and wall-like. Gastroscopic Diagnosis. Carcinoma of the pylorus.

Necropsy revealed metastatic carcinoma of the pylorus.

the ropelike sphincter muscle of the antrum. Immediately above on the lesser curvature was an ulceration. Its border toward the posterior wall was somewhat irregular. The intact mucosa joined it without elevation and was a vivid red. The anterior border showed two nodules which partly masked the yellow base. **Gastroscopic Diagnosis** Ulcer of the lesser curvature, probably carcinoma.

A biopsy was made. Operation revealed a tumor between the gastric angle and the cardia, which was resected. The ulcer measured 27 by 37 cm. Microscopic examination revealed that it was partly adenosarcoma and partly solid carcinoma.

**CASE 19**—A B, a worker by the day, aged 46, had lost weight and had pain in the stomach after meals. There was no free hydrochloric acid or occult blood in the stool. **Gastroscopy** At the angle of the lesser curvature there was an ulcerated tumor with raised margin. **Gastroscopic Diagnosis** Carcinoma of the lesser curvature.

A biopsy was made. Operation confirmed the diagnosis.

**CASE 20**—J R, a farmhand, aged 38, had lost weight, he had poor appetite and pain in the back. There was a palpable tumor of the stomach and blood in the stool. The condition was frank carcinoma.

**Gastroscopy** The anterior wall and lesser curvature protruded so far and so rigidly that they pressed against the optic and were not moved away by inflation. On a fold of the anterior wall a flat ulceration was surrounded by blood infiltration. **Gastroscopic diagnosis** was carcinoma of the anterior wall and lesser curvature.

In the following case the ulcer could not be brought to view. Only the neoplastic infiltration of the mucosa furnished the diagnosis.

**CASE 22**—G N, a helper, aged 57, had lost weight and had had severe gastric pain, after eating, of four months' duration. There was a palpable tumor. He had pyloric stenosis. Radioscopy yielded nothing definite, but clinically there was no doubt that the condition was carcinoma.

**Gastroscopy** There was a small dark brown mass in the fundus. There was a marked tumor prominence of the lesser curvature so large that it obstructed any view of the pyloric region. From the anterior to the posterior wall stretched a glistening mucous band partly infiltrated with blood. In the anterior wall of the lesser curvature, there was a fold bordered area, depressed and less glistening, with a peculiar gray and rigid appearance. **Gastroscopic Diagnosis** Scirrhus carcinoma of the lesser curvature. Biopsy revealed carcinoma of the lesser curvature, well advanced. It could not be resected because of metastases to the glands. Gastro-enteroanastomosis was performed.

**Necropsy** The same findings.

In the following case the gastroscopic picture was more distinctive than the macroscopic picture at necropsy. The final diagnosis was made by the microscope.

**CASE 23**—K S, a typesetter, aged 48, had lost weight and had gastric pain. Radioscopy revealed that there was probably carcinoma of the pylorus, and carcinomatous ascites. **Gastroscopy** High up on the lesser curvature there was a large deeply fissured tumor-like area. It was dirty gray-green or gray-yellow, the margin being somewhat raised. Further entrance by the gastroscope was impossible. **Gastroscopic Diagnosis** Carcinoma of the lesser curvature. At necropsy it was found that the mucosa was macroscopically unchanged. A tumor appeared to arise in the tail of the pancreas and infiltrate the stomach wall. Microscopic examination revealed adenocarcinoma of the stomach. The mucosa of the lesser curvature was extensively necrotic.



Necropsy revealed a sharply defined large necrotic, disintegrating carcinomatous ulcer of the pylorus

CASE 16—P R., a day laborer, aged 57, had lost weight and had had pain in the stomach, pyloric stenosis and blood in the stool. Gastroscopy. There was a rather long tumor of the greater curvature of the antrum with raised margin, extensively ulcerated. Across the ulcerated area stretched many tough threads of mucus.

Biopsy was performed. Operation revealed a carcinoma of the greater curvature at the pylorus, which was resected.

#### CARCINOMA OF THE LESSER CURVATURE

It is perhaps no accident that two "early" diagnoses proved to be carcinoma of the lesser curvature. By "early" diagnosis is meant a diagnosis made at a time at which the unquestionable recognition of carcinoma is not yet possible by methods other than gastroscopy and while the tumor is still operable.

CASE 17—A R., a watchman, aged 60, had no gastric symptoms. There were merely weakness and loss of weight. Three years before he had had tuberculosis of the right shoulder-joint. Five years before he had had pulmonary hemorrhage. He now had extensive indurated tuberculosis of the right upper lobe. He had marked anemia (hemoglobin, 38 per cent). The stools showed occult blood. Tuberculosis of the bowel was first suspected. There was no free hydrochloric acid. Radioscopy revealed a flabby stomach sagging toward the colon and diverticular outpouching of the greater curvature (malformation). The consulting surgeon refused surgical intervention because of doubtful diagnosis and the serious pulmonic lesion.

First Gastroscopy. There was a rigid spastic fold protruding from the anterior wall.

Second Gastroscopy. The pylorus was clearly focused. There was active motility, type 2.

As the pylorus contracted, a red half-spherical prominence appeared on the lesser curvature of the antrum cavity, half covering the latter during contraction, and having at its apex a small yellow point. When the pylorus relaxed, it disappeared behind the gastric curvature. This was observed for some time.

A biopsy was made. Operation was performed because of the foregoing findings. There was carcinoma (microscopic adenocarcinoma) of the lesser curvature not extending to the sphincter. A shallow ulcer with an elevated margin was resected.

The medical practitioner could without doubt often obtain equally satisfactory results by resorting to early gastroscopy in the case of gastric disease or of old people who are anemic and losing weight.

CASE 18—A N., a clerk, aged 54, had gastric pains after meals. He had lost weight and had vomited during five months. There was some mucus in the stomach after a test breakfast. There was no free hydrochloric acid and no blood in the stool. No tumor mass was present. Radioscopy revealed a rather long fish-hook stomach and marked peristalsis. Emptying of the stomach was somewhat retarded. There was no evidence of tumor. Duodenal stricture was suspected.

First Gastroscopy. The stomach contained large masses of thick glairy mucus, mixed with blood which obscured the view of the lower portion of the organ.

Second Gastroscopy. Excellent view was obtained. The pylorus contracted normally and completely (Type 1), expelling fluid. At the angle was

The following is the only finely nodular cauliflower carcinoma in my series

CASE 28—I O, a man, retired, aged 68, suffered from loss of weight, pain, vomiting and a palpable tumor

Gastrosocopy On the greater curvature of the corpus there was a projecting, finely nodular cauliflower growth There was bloody, fluid mucus  
Gastrosocopic Diagnosis, carcinoma of the corpus

The next case presents a maneuver in gastrosocopic technic which the beginner should never imitate

CASE 29—J K, a day laborer, aged 53, for the past six months had had gastric pain immediately after meals and he vomited There was no free hydrochloric acid or blood in the stool However, the diagnosis of ulcer with hour-glass stomach was made in two roentgen-ray institutes Clinically, however, the suspicion of carcinoma of the cardia remained

Gastrosocopy It was not possible to introduce the gastroscope as the rigid portion met an impassible obstruction at the cardia Therefore the obturator tube was withdrawn and the optic tube carefully pushed in, and although the mark was still somewhat above the teeth, it was possible to obtain a view The cardia arched forward, sickle-shaped Below was a crater-like sloping mucosa On the floor of the crater was an irregular ulcer covered with ragged dirty gray-yellow membrane Below was the cavity of the stomach From it dark Burgundy red fluid flowed over the ulcer  
Gastrosocopic Diagnosis Carcinoma of the greater curvature of the fornix

A biopsy was made Operation confirmed the diagnosis The cancer infiltrated the colon The colon and stomach were resected It was necessary to divide the lesser curvature immediately below the cardia

#### CARCINOMA BENEATH A GASTRO-ENTEROSTOMY OPENING

In this case, gastrosocopy accomplished a unique and brilliant diagnosis, an early diagnosis which has already been reported It will be mentioned only briefly here

CASE 30—E B, a shoemaker's wife, aged 44, had had an operation on the stomach eleven years before She had lost weight during the last two months and was anemic Radiosocopy revealed a functioning gastro-enterostomy Otherwise the examination was negative Clinical Diagnosis Suspicion of ulcer

Gastrosocopy In the deepest portion of the fundus, there was a collection of ragged gray-yellow masses floating in fluid On the greater curvature, there was an oval opening which opened and closed rhythmically On closing, it discharged the same shreddy material seen in the fundus On its upper margin, there were two small yellow-coated ulcers In the pyloric region there was a binodular polypoid excrescence The pylorus was not visible  
Gastrosocopic Diagnosis Malignant tumor immediately beneath a gastro-enterostomy—peptic ulcer

A biopsy was made Just previous to the operation it was learned that the pylorus had been resected eleven years before because of carcinoma The old microscopic preparation confirmed it There proved to be a carcinomatous recurrence in the colon beneath the gastro-enterostomy opening which it was possible to resect, together with the ulcers and the stump of the pylorus

## CARCINOMA OF THE FUNDUS

Carcinoma of the fundus occasionally renders the introduction of the instrument exceedingly difficult, especially so the higher up it is located. Gastroscope of carcinoma of the cardia is obviously not feasible. Esophagoscopy is the method to be used.

CASE 24—F B, locomotive engineer, aged 58, had lost weight and appetite and had gastric pain. Examination revealed no free hydrochloric acid. There was much blood in the stool. Radioscopy revealed a tumor-like bulging on the anterior wall. Between this and the posterior wall there was a small fissure on the greater curvature discharging blackish green fluid. Below the conical bulging of the front wall there was a nodular red excrescence. *Gastroscopic Diagnosis* Carcinoma of the posterior wall and greater curvature of the fundus. A biopsy was performed. Operation revealed carcinoma at the site specified. The tumor was resected.

CASE 25—M D, a coachman, aged 60, had lost weight and had gastric pain. There was no free hydrochloric acid, or blood in the stool. Radioscopy revealed a probable tumor.

*Gastroscope* It was not possible to obtain a clear view of the anterior wall of the lesser curvature of the fundus because of the close proximity of the instrument to this surface. By moving the prism downward to the right with the patient in the left-sided position, the extremely pale mucosa was seen to be injected with small hemorrhages. To the left was a large prominent brownish violet tumor. *Gastroscopic Diagnosis* Carcinoma of the anterior wall and greater curvature of the fundus. Necropsy confirmed the diagnosis.

The following case shows that the gastroscopic finding may be of importance as an indication for treatment.

CASE 26—Bertha A, a cook, aged 27, had had hypogastric pain for six weeks. Five months before bilateral ovarian carcinomas had been removed. A few weeks later there were symptoms of ileus. Now there was a recurrence in the pelvis, compressing the rectum. It was the intention to give deep roentgen-ray treatment, but radioscopy of the stomach and bowel showed, besides dilatation of numerous intestinal loops, a defect of the greater curvature. Irradiation should be used only when the stomach is not involved.

*Gastroscope* The anterior wall, lesser curvature and pyloric region were rigidly infiltrated. The antrum presented a rigid trough. The pylorus was not patent. On the greater curvature of the fundus is a grayish-red ulceration with a high wall-like margin. *Gastroscopic Diagnosis* Carcinomatous ulcer of the greater curvature, probable extensive infiltration of the stomach wall.

It follows that the ovarian carcinomas were metastases from the primary gastric cancer. The treatment was purely symptomatic, irradiation being discarded. Necropsy fully confirmed the diagnosis.

CASE 27—C K, a mason, aged 51, had profuse hematemesis without loss of weight or definite symptoms. *Diagnosis* Probably round ulcer. The stools were free from blood after four weeks. Three weeks later there was vomiting and no free hydrochloric acid.

*Gastroscope* The anterior wall was difficult to focus. The posterior wall was very well focused. Just below the cardia there was the elevated margin of a fissured yellowish white ulcer of the greater curvature. The wall presented rough nodules and depressions. *Gastroscopic Diagnosis* Carcinoma of the corpus. Radioscopy confirmed the diagnosis. Necropsy revealed carcinoma of the corpus, perforating into the liver.

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## 'THE GENERAL RELATION BETWEEN SUSCEPTIBILITY AND PHYSIOLOGIC CONDITION'

C M CHILD, M D

CHICAGO

The pharmacologist and the student of mammalian physiology find in general a high degree of apparent specificity in the susceptibility of different organs and parts to drugs and other external agents. For example, strychnin and atropin in certain concentrations are both excitants of the central nervous system, but strychnin is believed to act chiefly on the spinal centers, while atropin apparently affects chiefly the higher centers. Again, agaricin supposedly inhibits the terminations of the secretory fibers of sweat glands, but not, or to a lesser degree, other secretory terminations, but atropin is believed to inhibit not only the secretory terminations of the sweat glands, but also those of many others. Pilocarpin, on the other hand, supposedly excites the terminations of secretory nerves. The susceptibility of sensory nerves to cocaine is apparently greater than that of motor nerves. In the susceptibilities of different parts of the nervous system and other organs to various anesthetics and narcotics, for example, ether, chloroform, morphin, nitrous oxid, etc., certain apparently more or less specific differences appear. The action of digitalin and related drugs on the heart and central nervous system and the action of ergot on the pregnant uterus are further cases in point.

Moreover, the susceptibility relations to a particular agent may differ greatly with different concentrations. A low concentration may excite a particular organ or part, a higher concentration may inhibit it. Certain concentrations may apparently be without effect on certain organs, although affecting others to a marked degree, while other concentrations may affect all. Of course, in the higher animals and man it is usually impossible to determine with any accuracy the concentration of an agent to which a particular internal organ is exposed at a given time. This is in general true whether the agent is introduced through the alimentary tract, the blood stream, the lymph, or from the body cavity. Some of the apparent specificities in the susceptibilities

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\* From the Hull Zoological Laboratory of the University of Chicago

In this connection it may be mentioned that another case came to operation in which the radiosopic diagnosis of carcinoma was made while nothing was found with the gastroscope. At operation the stomach revealed no pathologic change.

#### SUMMARY

Four benign and twenty-six malignant gastric tumors were demonstrated by gastroscopy. Of the four benign tumors two were fibromyomas, one solitary mucous polyp and one polyposis.

Of the twenty-six malignant tumors, one was diffuse lymphosarcoma and twenty-five carcinoma. Ten were confirmed by biopsy, eleven by necropsy, two by biopsy and necropsy. The findings were always in full accord. In three cases, early diagnosis of carcinoma was possible.

Through systematic employment of this modification of the gastroscope, I hope that early diagnosis of carcinoma will be definitely advanced.

which this process occurs. The cells of certain body regions or of certain individuals may lose their characteristic structure and break down completely, while those of other regions or individuals are still intact and show ciliary, contractile or other activity as evidence of life. With other agents or in other forms a coagulation of the protoplasm may serve as an indicator of death and so of susceptibility. Cessation of motor activity in motile forms, a certain degree of narcosis or of some other toxic effect of an agent can also be used in some cases as criteria of susceptibility.

In work of this sort with chemical agents it is of course necessary to provide so far as possible for equal exposure to the agent of different body regions which are to be tested. In naked aquatic forms with little differentiation of different regions of the body surface, for example, many flatworms the free swimming blastulae, gastrulae and larval stages of many invertebrates, the susceptibilities of different regions of the surface to chemical agents can be directly determined without difficulty, in solutions of the agents. In more highly differentiated forms with internal organs, the susceptibilities of these organs to chemical agents cannot be directly determined simply by immersing the organism in the agent used, because the agent must pass through or disintegrate the surface of the body before it can act on the internal organs. In many of the lower invertebrates, this difficulty can be in part eliminated by exposing transverse cut surfaces from different levels of the body, or from the same levels of different individuals, and in some forms in which a cuticle or other nonliving layer covers the surface, transverse cut surfaces may also be used. In many of these cases, however, it can be shown by comparing the effects of various chemical and physical agents that regional differences in susceptibility are independent of the cuticle, for example, we may find that the differences are similar for extremes of temperature and lack of oxygen, on the one hand, and potassium cyanid or hydrochloric acid on the other. It is evident that with certain physical agents, such as extremes of temperature, the impermeability of a surface covering is not of importance.

In the investigation of susceptibility in early developmental stages it is also generally possible to make use of the action of external agents on the rate of development as well as of their directly lethal or toxic action. For example, the inhibiting or accelerating effect of different agents on different body regions may be determined and compared.<sup>2</sup>

These various ways of determining susceptibility are all modifications of what has been called the direct method, because the susceptibility is directly determined by the lethal, toxic or other action

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<sup>2</sup> References 2, 3, 14 and 19

of different organs to certain agents are probably due to the fact that the different organs are actually subjected to widely different concentrations

A distinction is often made between agents which affect only or chiefly certain organs or complexes, and the general protoplasmic poisons, such as the cyanids, the stronger acids, formaldehyd, phenol, salts of mercury and copper, etc. Many such agents are used as antiseptics. This distinction appears, however, to be chiefly, if not wholly, one of degree rather than of kind, for, so far as we know, any physical or chemical agent which acts on living protoplasm will become in sufficient concentration or intensity and with sufficient time a general protoplasmic poison, although the susceptibility to it of different species of organisms and of different organs may differ widely.

Without questioning the existence of the significance of specificities in susceptibility to external agents, particularly in the higher animals and man, it is my purpose to call attention to another aspect of the susceptibility problem which has become evident in the course of about twenty years of physiologic work on the lower invertebrates and on early developmental stages of both invertebrates and vertebrates. In these forms and stages we find a general and highly uniform relation in different individuals of the species and in different regions of the individual between susceptibility to many, perhaps to all, external agents in a certain range of concentration or intensity, and quantitative factors in physiologic or metabolic condition. Although this essentially quantitative relation between susceptibility and physiologic condition may undergo extensive modification in the course of development, particularly in the higher animals and man, it apparently constitutes the general physiologic foundation on which the more or less specific, or apparently specific, susceptibilities of the more highly specialized organs and parts develop.

I shall attempt to bring together in the form of a brief survey with references the more important facts and conclusions from this field of general physiology.

#### CRITERIA OF SUSCEPTIBILITY AND METHODS OF INVESTIGATION

With a certain range of concentration or intensity, susceptibility can be determined by survival time in many organisms. At all stages in many of the simpler organisms and in the earlier stages of development, even of the vertebrates, the occurrence of death through the action of a certain range of concentration or intensity of a large number of agents is closely associated with cellular disintegration or cytolysis.<sup>1</sup> Differences in susceptibility are indicated by differences in the time at

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<sup>1</sup> References 4, 6, 8, 11, 13, 19, 22, 32, 33, 35, 45, 51 and 52 in the literature cited

activity or its rate of growth and development are more inhibited than those of others in somewhat lower concentrations, the different lines of evidence serve to confirm each other. But the chief interest of the susceptibility method for general physiology is the wide field within which the regional differences in susceptibility within the individual and the individual differences within the species are nonspecific, or specific only to a slight degree, for particular agents. The factors concerned in these differences are discussed in the following sections.

#### EXPERIMENTAL DATA AND CONCLUSIONS

The general susceptibility relations have been studied in several hundred species of animals and plants. Stated briefly, the general conclusions are as follows. To a certain range of concentration or intensity of action of agent above the limit of acclimation and either lethal in the course of a few hours, or producing irreversible changes when exposure is continuous or changes only slowly reversible when exposure is temporary, susceptibility varies in general directly with, though not necessarily proportionally to, the rate of oxidative metabolism. To certain lower ranges of concentration or intensity of action the ability to acclimate or acquire tolerance varies in general directly with, though not proportionally to, the rate of oxidative metabolism. And finally, the ability to recover after temporary exposure to a certain range of concentration or intensity shows the same relation to oxidative metabolism.

In certain cases it has been possible to check the data on susceptibility by direct determination or colorimetric estimation of respiratory exchange of different body regions and individuals. In many other cases an indirect check has been obtained by comparison between susceptibility to potassium cyanid and the effect of this agent on oxygen consumption.<sup>7</sup> Regional and individual differences in rate and amount of reduction of potassium permanganate by protoplasm afford another check,<sup>8</sup> the indophenol reaction has proved useful in certain cases,<sup>9</sup> and differences in electric potential constitute at least an indicator of differences in physiologic condition.<sup>10</sup> In addition to these experimental methods, differences in rate of growth and development and of protoplasmic structure often serve as further indicators of difference in physiologic condition.<sup>11</sup> So far as facts are at hand, the evidence from all these different lines agrees for the earlier develop-

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7 References 1, 7, 9 Chap III to VIII, 23, 24, 34, 37, 38, 39, 40, 41, 42, 44, 46 and 47

8 References 21 and 29

9 Reference 8

10 References 43 and 48

11 Reference 10, Chap III



of the agent<sup>3</sup> The range of concentration or intensity available for this method lies between that which is immediately lethal for all parts or individuals concerned and that which permits the acquirement of tolerance by some regions or individuals

But susceptibility can also be determined indirectly, that is, by determining the ability to acclimate<sup>4</sup> or acquire tolerance to a certain low range of concentrations or intensities, not lethal within a short time, and by the ability to recover after temporary exposure to a nonlethal range In mature forms such acclimation or recovery may be indicated by continuation of life, resumption of motor activity, increase in respiratory exchange after an initial decrease, or by other physiologic criteria In early developmental stages it may also be indicated by increase in rate of growth or differentiation after an initial inhibition<sup>5</sup> This method of investigating susceptibility through the ability to acclimate to, or to recover from, the action of an agent has been called the indirect method<sup>6</sup>

To obtain adequate knowledge of the susceptibility of a particular organism to a particular agent in relation to physiologic condition it is necessary to work with a wide range of concentrations or intensities from those which are rapidly lethal to those which permit rapid acclimation or recovery by the most susceptible individuals or parts concerned Moreover, some agents have different lethal or toxic actions in different concentrations For example, mercuric chlorid in high concentrations "fixes" protoplasm, while in low concentration it disintegrates many protoplasts, and in still lower concentration it permits continuation of life and acclimation Also the range of concentrations producing each of these effects differs in a definite way with differences in physiologic condition for different body regions of the individual and different individuals of the species In a study of susceptibility of developmental stages of the frog to mercuric chlorid, it was found necessary to use concentrations ranging from  $\frac{1}{5,000}$  to  $\frac{1}{30,000,000}$  molar

These various modifications of the direct and indirect methods of determining susceptibility make possible various checks on the results of any one of them If, for example, a certain body region is killed earlier than others in a high concentration and its motor or respiratory

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3 References 1, 2, 4, 6, 7, 8, 9, 11, 13, 14, 15, 16, 19, 22, 25, 32, 33, 35, 45, 51 and 52

4 The terms "acclimate" and "acclimation" are used here in the general biologic sense denoting adjustment or equilibration to an environment Acclimation, as the term is used in this paper, is essentially the same as acquirement of tolerance except that in the work with the simpler organisms the agent is usually added directly to the normal environmental medium

5 References 14 and 19

6 References 4, 7, 9 Chap III, and 14

the species the differences in susceptibility depend in general primarily on quantitative differences in physiologic condition and only secondarily on the specific differences in the constitution of different organs and parts arising in the course of development

#### THE PRIMARY REGIONAL AND INDIVIDUAL DIFFERENCES IN SUSCEPTIBILITY

In general, the earliest stages of development following fertilization are periods of acceleration of oxidative metabolism, as has been shown by Waibung, Loeb Meyerhof and others, but early in the development a maximum is reached, and from this time on the rate of oxidative metabolism shows, on the whole, a decrease with the further progress of development and the advance of physiologic age. The changes during development in susceptibility and the capacity for acclimation and recovery parallel in general these changes in metabolic rate.<sup>14</sup> In the development of many forms, however, the decrease in rate of oxidative metabolism is not uniform and continuous, but is interrupted by periods of increase in rate at certain stages of development. These periods of increase are determined by various factors, for example, the appearance of motor activity, rapid growth of certain parts, some forms of larval metamorphosis, sexual maturity or breeding periods and various other functional factors. In the simpler organisms these changes are paralleled by corresponding changes in susceptibility, except so far as the general susceptibility relations are complicated and altered by the appearance of more or less specific susceptibilities of particular organs to particular agents.

In the flatworm, *Planaria*, and in various other animals which do not die after a short period of starvation but live on their tissues and decrease in size, an increase in rate of respiratory exchange occurs in the more advanced stages of starvation. Susceptibility likewise increases, and after feeding is resumed the susceptibility and rate of respiration are equal to, or somewhat higher than, a growing well fed animal of the same size as the animal reduced by starvation.<sup>15</sup> Similarly, the reorganization of an isolated piece of *Planaria* and others of the simpler animals into a new complete individual, and many, if not all of the processes of asexual reproduction, are accompanied by an increase in rate of respiratory exchange and an increase in susceptibility.<sup>16</sup> In short, susceptibility gives a rough comparative measure of physiologic age and indicates the occurrence of rejuven-

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14 References 7, 9, Chap IV, V, VI and XV, 20, 39, 40 and 50

15 References 7, 9 Chap VII, 24, 38 and 42

16 References 9 Chap V and VI, and 39

mental stages in general and for most of the simpler organisms, both animal and plant, throughout life. Exceptions and discrepancies have been shown in so many cases to be secondary results of the progress of differentiation and to be absent in the earlier developmental stages that we are justified in believing that for the protoplasm of a particular species the regional and individual differences in susceptibility depend primarily on quantitative factors in the protoplasm, and that the more or less specific relations between particular organs and particular agents which are characteristic of the higher animals and of man are secondary results of differentiation.

The following agents have been used thus far in work on susceptibility: potassium cyanid, various anesthetics including ethyl alcohol, ether, chloroform, chloroform, ethyl urethane, phenyl urethane, hydrochloric acid, sulphuric acid, acetic acid, sodium hydroxid, ammonium hydroxid, lithium chlorid, mercuric chlorid, copper sulphate, magnesium sulphate and many other electrolytes, the alkaloids caffeine and strychnin, the "vital" dyes neutral red and methylene blue, hypotonic sea water for marine forms and distilled water for fresh water forms, the negative condition, lack of oxygen, extremes of temperature and light.<sup>12</sup> By no means all of these agents have been used on every form examined, but in practically all cases several of them have been used. Potassium cyanid and ammonium hydroxid have been extensively used, first, because their high toxicity makes it possible to work with very low concentrations, second, because the death changes produced by these agents in most protoplasms involve a disintegration of the cells which is readily observed, and third, in the case of potassium cyanid, because its inhibitory action on respiration and protoplasmic oxidation<sup>13</sup> gives the differences in susceptibility to cyanid an additional value as evidence of differences in oxidative rate.

It is scarcely necessary to say that for different species the concentrations or intensities and the time necessary for a particular effect differ widely. The protoplasm of each species has its own range of susceptibility and limits of acclimation and recovery and the order of effectiveness of different agents is not necessarily exactly the same for different species. That is to say, the susceptibility of each species-protoplasm, and perhaps to some degree that of each variety, race or pure line, is more or less specific, but the evidence indicates that within

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<sup>12</sup> Experiments with ultraviolet light and with light of the visible spectrum after sensitization of the organisms made at the Nela Research Laboratories by Dr. Marie Hinrichs under the direction of Dr. R. S. Lillie show the same general differences in susceptibility to light as to other agents. Through the kindness of the Nela Laboratories and Dr. Hinrichs I am permitted to mention here this unpublished work.

<sup>13</sup> References 23, 34, 37, 41 and 44.

groups, physiologic polarity has been found without exception to be represented by such a gradient in susceptibility to many different agents. So far as evidence is at hand, the same is true for axes of radial and bilateral symmetry and for axes of particular organs.

The question of the origin of such gradients cannot be considered at length here, but it may be noted that a large amount of experimental evidence, as well as the facts of development, show that in the final analysis the gradients arise through exposure of the protoplasm concerned to a quantitative differential in environmental conditions<sup>18</sup>. Such differentials may be either intra-organismic or external. By various experimental methods it is possible to establish new gradients in many cases and so to determine new axes of polarity and symmetry.

In consequence of the differential susceptibility along an axis it is possible to alter experimentally the slope of the gradient and even to obliterate it. In this way the course of development as regards polarity and symmetry can be modified and controlled, and these axes can be completely obliterated so that the organism becomes apolar or even anaxiate<sup>19</sup>. The evidence for nature, origin and modification of these axial physiologic gradients is given in the references cited in Footnote 17.

Since the early stages of development of the sea urchin and of closely related forms have served as material for considerable work on susceptibility, a brief statement of the more important results attained will serve to show what can be accomplished by means of the susceptibility methods. In the unfertilized egg and the cleavage stages a gradient in susceptibility is present, although the absence of visible landmarks in some stages makes it impossible to demonstrate completely that the gradient always represents the polar axis. But from the elongated blastula stage on there is no difficulty. The elongated blastula is an ovoid form consisting of a single layer of cells surrounding an internal cavity, the wall being slightly thicker at the basal than at the apical end. This minute larva swims by means of cilia, with the apical end in advance. The differential susceptibility of this blastula stage, as well as that of other stages, has been studied by means of the following agents in concentrations empirically determined: Potassium cyanid, ethyl alcohol, hydrochloric acid, acetic acid, potassium permanganate, sodium hydroxid, mercuric chlorid, copper sulphate, hypotonic sea water, neutral red and crowding (lack of oxygen or accumulation of carbon dioxide). In a certain range of concentration of all these agents the toxic action, as indicated by cytolytic change or disintegration of the cells, occurs first at the apical

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18 Reference 27, Chap. III

19 Reference 14

escence in early embryonic development in starvation, in reconstitution and in asexual reproduction as clearly as does the rate of respiratory exchange

Within the individual the differences in susceptibility serve primarily as indicators of the chief physiologic axes. The evidence from susceptibility, checked and confirmed by experimental data on respiratory exchange, reduction of potassium permanganate, electric potential differences and by observational data on rate of cell division, differentiation and growth, indicates that a physiologic axis is primarily a gradient in rate of the fundamental metabolic reactions concerned in living, with which are associated corresponding gradients in aggregate condition of the protoplasm, permeability of membranes and probably also gradients in water content and various other factors in protoplasmic condition<sup>17</sup>. In the work on susceptibility these gradients are indicated, either directly by disintegration or other changes associated with toxic action of the agent, or indirectly by differences along an axis in ability to acclimate to or recover from the toxic action. A brief survey of the data concerning the polar axis will serve as an illustration of results obtained with the susceptibility method. All except perhaps some of the simplest organisms possess what is called physiologic polarity, that is, organs develop and are arranged in a definite order with reference to a line which we call the polar axis. One end of this axis becomes the apical end, or in bilateral animals, the head, the other the basal or posterior end. This polar axis appears primarily as a quantitative gradient in physiologic condition as indicated by differences in rate of respiratory exchange, reduction of potassium permanganate, electric potential differences and susceptibility. In this gradient, susceptibility to higher concentrations and intensities and capacity for acclimation to and recovery from action of lower concentrations and intensities is greatest at that end of the gradient or axis from which the apical end or head of the organism arises and decreases posteriorly. Here also the results of the susceptibility method parallel those obtained by other methods in indicating that the high end of the gradient, that is, the region of highest physiologic activity, becomes apical or anterior and that other organs along the axis are localized at particular levels of the gradient. During the course of development this simple primary gradient may undergo modification and complication through the appearance of new gradients as particular organs and parts develop, and in some cases the primary polar gradient may even disappear and be replaced by others. Nevertheless, among several hundred species of animals and plants, including representatives of all the great animal

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17 References 2, 3, 4, 5, 6, 8, 9 Chap. IX, 10, 11, 13, 14, 15, 16, 17, 18, 19, 21, 22, 25, 26, 27, 28, 29, 30, 31, 32, 33, 35, 36, 43, 45, 46, 48, 49, 51 and 52

Work on modification of reconstitution in planarians,<sup>21</sup> on developmental modification in amphibia by Bellamy<sup>22</sup> and unpublished work on fishes by Mr J N Gowanloch, as well as data on many other species, show that the differences in susceptibility are primarily similar in their relations to the chief body axes in very different organisms, both animals and plants, for certain ranges of concentration or intensity of all agents thus far used

#### THE PHYSIOLOGIC BASIS OF GENERAL SUSCEPTIBILITY

The experimental data presented above may seem at first glance to be in direct conflict with the data from mammalian and human physiology and pharmacology, but it is my purpose to show that this is not the case

In the first place, it is of course evident that external agents do not all act on living protoplasms in the same way. While our knowledge of the physicochemical changes concerned in the toxic or lethal action of any agent is far from complete, it is evident that different agents produce their effects in different ways. The action of acids and alkalis of high and low extremes of temperature, of lack of oxygen and of accumulation of carbon dioxide cannot be identical. Again, the action of a heavy metal salt, such as mercuric chloride, of various anesthetics, such as ether, chloroform, etc., of "stimulating" alkaloids, such as caffeine, and of vital dyes, such as neutral red, must differ in many respects. Some agents may affect primarily the aggregate condition of the colloids, others the nature, concentration or balance of ions. Still others probably act primarily in one way or another on the lipoids, the action of some is chiefly osmotic, some may combine chemically with certain constituents of the protoplasm or enter into the chemical reactions of metabolism, and so on. Moreover, a particular agent may act differently on the protoplasms of different species or of different, highly specialized organs according to their constitution.

If we admit, as we must, these different possibilities of action, it is at once evident that the general susceptibility relations described in the preceding sections are quite independent of the specific character of the action of a particular agent. Moreover, the nonspecific character of the axial and regional differences in susceptibility within the individual and the individual differences within the species or race indicate that they depend primarily, not on the nature of the action of the various agents, but on some quantitative factor in the organism itself.

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<sup>21</sup> References 4, 12 and 28

<sup>22</sup> References 2 and 3

end and progresses basipetally. In somewhat later stages, as bilaterality develops, the basipetal progress of death is most rapid along that meridian which later becomes the anterior end of the larva. The method serves further not only to demonstrate the existence of the axial gradients, but also in many cases to pick out regions of rapid growth as they arise in development. In the more advanced stages, however, the possibility of modification of the primary quantitative relations by the appearance of specific susceptibilities exists, although it is practically excluded when similar results are obtained with a large number of different agents. Motor activity increases and quiescence decreases susceptibility. These data on the sea urchin have been published only in part <sup>20</sup>

But instead of using the agents to kill, we may also investigate sea urchin susceptibility by subjecting early developmental stages to somewhat lower concentrations of agents, or for certain periods of time, and observing the modifications of development which occur. I have performed experiments of this kind with all the agents mentioned above <sup>19</sup> and Dr J W MacArthur has performed such experiments with a large number of electrolytes, and in all cases it has been found that with certain ranges of concentration the development of the apical region is more inhibited than that of the basal region, and in later stages that of the median anterior region more than that of posterior and lateral regions. The most inhibited regions are smaller as compared with the normal than those less inhibited, or with the more extreme degrees of inhibition may fail entirely to develop. With concentrations permitting acclimation or recovery after temporary exposure, the apical and median anterior regions acclimate or recover more rapidly or more completely and so become relatively larger—as compared with the normal—than basal, posterior and lateral regions. By means of certain “stimulating” or accelerating agents in certain concentrations or intensities, for example, caffeine (Hinrichs), a differential acceleration of development can be produced. In such cases apical and median anterior regions are more accelerated and relatively larger than basal, posterior and lateral regions. In these various ways modifications of form in two opposite directions and essentially similar in character for all the agents used can be obtained. The more extreme differential inhibitions are so different from the differential acclimations, recoveries and accelerations that they would not be recognized as belonging to the same species were their origins not known <sup>19</sup>. With a sufficient degree of differential inhibition bilaterality is obliterated or prevented from arising, and with a still greater degree polarity is also obliterated <sup>19</sup>

may be a factor in susceptibility to the direct toxic or lethal action of certain agents, it is evident that the nonspecific aspects of susceptibility in general cannot be accounted for in terms of permeability alone.

It has been stated above that the data at hand indicate a parallelism between susceptibility to toxic action and capacity for acclimation and recovery on the one hand and rate of oxidative metabolism on the other. Even if this be granted, it is evident that the oxidation-reduction reactions cannot be directly responsible for the parallel differences in susceptibility to so many different agents and conditions acting in so many different ways.

Where, then, shall we look for the physiologic basis of these general, nonspecific aspects of susceptibility? In view of all the facts, the only possible conclusion seems to be that the basis is to be found in a general relation between dynamic systems and external agents or conditions which produce disturbance or alteration of such systems. This general relation, which holds for nonliving as well as for living systems, may be stated for our purposes in the following terms. To disturbances producing in any manner alteration beyond the limits of equilibration or tolerance of the system and therefore leading to disruption or other irreversible change within a measurable period of time, the susceptibility must vary directly with, though not necessarily proportionally to, the rate of the changes characteristic of the system. On the other hand, to disturbances within the limits of equilibration, acclimation or tolerance, or to those producing changes which are reversible after the disturbance ceases to act, the ability of the system to equilibrate, acclimate or acquire tolerance must also vary directly with, though not necessarily proportionally to, the rate of activity within the system. The facts presented above force us to the conclusion that the susceptibility of living protoplasmic systems to certain degrees of external disturbance of at least many, if not of all, sorts is merely a special case of this general relation between dynamic systems and external disturbances.

On this basis the nonspecific character of the differences in susceptibility with respect to different agents receives a simple physico-chemical interpretation. No matter in what particular way the agent acts, if the degree of action is adequate to produce death or irreversible change in a measurable period of time, the more active region or individual must be more susceptible, and if its action is within the limits of acclimation, tolerance or recovery, all of which are processes of dynamic equilibration, the more active region or individual will acclimate or recover more rapidly or more completely than the less active.

The parallelism between susceptibility, acclimation and recovery and rate of oxidative metabolism observed or indicated in cases thus



In the light of present knowledge concerning permeability of protoplasmic membranes the possibility that differences in permeability may be responsible for at least some of the nonspecific differences in susceptibility at once suggests itself. As a matter of fact, axial, regional and individual differences in permeability to many agents undoubtedly exist. Gradients in penetration of vital dyes corresponding to the susceptibility gradients have been shown to exist in many forms,<sup>23</sup> and there are indications that similar penetration gradients for many other substances occur. But when we consider the data of susceptibility it is evident that differences in permeability will not account for all the facts as they stand. Even if we admit that the regions representing the higher levels of the axial gradients of susceptibility are in general more permeable than those representing the lower levels, there can still be no doubt that other factors than permeability are of fundamental importance in determining the susceptibility relations. In the first place, these relations are essentially similar in different organisms, both for agents such as vital dyes, which readily penetrate living protoplasmic membranes and exert their toxic action by accumulating within the cells, and for agents such as mercuric chlorid, which do not penetrate in appreciable quantities without killing or altering the membranes and their permeability. Moreover, the permeability of living membranes depends on the fact that they are alive, and living systems are dynamic, not static, that is, they are systems in which physicochemical changes are going on in or with approach to dynamic equilibrium. Therefore the permeability of living membranes must itself be in some measure an expression of the physicochemical activities, of the dynamic equilibrium or equilibration processes in the membranes. Consequently differences in permeability are generally associated with differences in rate of activity of living systems.

In the case of susceptibility to certain agents or conditions, however, permeability is not directly concerned. For example, the differences in susceptibility to lack of oxygen and to extremes of temperature can scarcely be regarded as due primarily to differences in permeability, yet they are in general similar to those observed with chemical agents. And finally, capacity for acclimation cannot be accounted for in terms of permeability, for the regions and individuals that are more susceptible to the more extreme degrees of action of the agents show greater capacity for acclimation to the less extreme degrees of action. If such regions or individuals are more permeable to the agents concerned, acclimation must occur, not because of, but in spite of, their higher permeability. In short, while differences in permeability

cell To a sufficient degree of disturbance, therefore, we may expect to find it more susceptible than other cells of the body, and it should also possess greater ability to acclimate to or to recover from less extreme disturbances Its high susceptibility to the action of radium may be, therefore, largely or wholly nonspecific and merely another special case under the general law

In conclusion, one point must be emphasized, namely, that there is no necessary conflict between what has here been called the general law of susceptibility and the existence of specific relations between particular protoplasms, whether species or organs, and particular external agents The susceptibility of each species to external disturbances is undoubtedly in some measure specific, as is the susceptibility of any other dynamic system, but within the species the general law of susceptibility holds except as relations may be modified by specialization As species undergo specialization in the course of evolution, the susceptibilities of their protoplasms undoubtedly become more highly specific Similarly, as organs undergo specialization in development, their susceptibilities undoubtedly attain a higher specificity The general law of susceptibility concerns only one aspect, the nonspecific aspect of the relations between dynamic systems and external disturbances So far as different kinds of systems exist in the different regions or organs of an organism, so far the possibility of specific differences in susceptibility exists But within each particular kind of system the general law may still hold, its validity being again limited by specialization of the various parts of such a system into systems of particular kinds

#### SUMMARY

1 Evidence is presented in support of the conclusion that the susceptibility to action of external agents of the living protoplasms of different individuals of a species and of different regions of the individual depends primarily on quantitative differences in the individuals or regions concerned and that rate of oxidative metabolism is in some degree a measure of these differences The evidence at hand indicates that susceptibility and capacity for acclimation and recovery vary in general directly with, though not necessarily proportionally to, the rate of oxidative metabolism

2 This general law of susceptibility does not depend on the particular character of the action of a particular agent, but is a special case of the relation between dynamic systems and external disturbances It has been shown to hold for the simpler organisms and for the earlier stages of development and does not exclude the possibility that the susceptibilities of different species protoplasms and of different specialized organs, particularly in the more highly differentiated forms, are specific

fact examined does not necessarily mean that the external disturbing factor acts directly on the oxidation-reduction reactions. It merely means at most that the rate of these reactions is to some degree a measure of the activity of at least the less highly specialized protoplasmic systems, and it is primarily with such systems that we are concerned.

To what extent the apparently specific susceptibilities of particular organs to particular agents in the more highly specialized organisms and stages of development will be resolved by further experimental investigation into special cases of this general law of susceptibility, it is, of course, impossible to predict. Without considering details, it may be pointed out that various data indicate a higher susceptibility of the more anterior levels of the central nervous system to various agents, even in man and mammals, and in various axiate organs, such as the heart, there is also evidence of a gradient of susceptibility similar to that in the axes of simpler organisms. A particular organ or organ complex may have a specific protoplasmic constitution, but so do the protoplasms of different species, and the general law of susceptibility may apply within the specific organ in much the same way as within the species. On the other hand, it is by no means necessarily true, either for different species or for different organs, that the differences in susceptibility parallel the differences in rate of oxidative metabolism of their protoplasmic systems.

It must also be borne in mind that the simple axial gradients of earlier developmental stages may undergo many modifications or may even disappear in the course of development of the higher animals. In consequence of such modifications even the general nonspecific susceptibilities of different regions or parts may be very different in the mature animal from those in the early stages of development. Moreover, the occurrence of such modifications can be determined only by extensive experimental investigation of the various developmental stages.

The higher general susceptibility and the greater ability to acclimate and recover of the young as compared with the old organism are sufficiently evident in man and the mammals, and are taken into consideration in the administration of drugs in medical practice. Here the general parallelism between susceptibility, tolerance and recovery on the one hand, and rate of oxidative metabolism on the other, exists to some extent as in the simpler organisms.

It may be suggested also that the general law of susceptibility holds to some extent with respect to roentgen rays and radium, and particularly as regards the difference in susceptibility of the cancer cell and the other cells of the body. The cancer cell is an extremely active cell, being in this respect comparable to a physiologically young or embryonic

# GASTRIC ULCER AND ACHLORHYDRIA

J R BELL, M D (Melbourne), M R C P (London)

LONDON, ENG

Gastric and duodenal ulcer are frequently discussed under the heading of "peptic" ulcer, and there is no doubt that many of their hypothetical etiologic factors and clinical manifestations bring them into close relationship. The use of this general term, however, is by no means always advisable and leads to deductions that are not only confusing but erroneous. Statistics have been published under such a heading concerning the variations in the secretory and motor activities of the stomach, no attempt being made to discriminate between the two types of ulcer. Information thus obtained is valueless, for in these respects gastric and duodenal ulcers are markedly dissimilar. There is much evidence to support Hurst's<sup>1</sup> view that the motor activities of the stomach differ in the two conditions.

Since the introduction and widespread adoption of the fractional method of analysis of the gastric contents, it has become necessary to modify and even to abandon many of our former beliefs regarding the alterations in acidity in gastric and duodenal ulcer. This method, despite its present limitations and inaccuracies, supplies far more complete and reliable information than was obtained by means of the "one hour" test meal.

It was the general opinion that both types of ulcer were most frequently associated with a hyperacidity. Unquestionably, symptoms regarded as characteristic of this secretory disturbance were present in the majority of these cases, but the fact, as yet insufficiently appreciated, that these so-called symptoms of hyperacidity, including the immediate relief of abdominal distress obtained by taking alkalis, may occur in the complete and continued absence of free hydrochloric acid in the gastric contents, compels reconsideration of such a view.

Hurst,<sup>2</sup> in 1911, introduced 4 ounces (125 gm) of 0.5 per cent hydrochloric acid into the empty stomachs of six patients with proved gastric ulcers without producing any sensation. Bolton,<sup>3</sup> in 1913, stated that the pain of gastric ulcer did not bear any relation to the degree of acidity of the gastric contents, and might be relieved by food whether the acidity was normal or increased, and Carlson,<sup>4</sup> in 1918,

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1 Hurst, A F. New Views on Pathology, Diagnosis and Treatment of Gastric and Duodenal Ulcer, *Brit M J* **1** 559 (April 24) 1920.

2 Hurst, A F. The Sensibility of the Alimentary Canal, London, 1911.

3 Bolton, C. Ulcer of the Stomach, London, 1913.

4 Carlson, A J. Origin of Epigastric Pains in Cases of Gastric and Duodenal Ulcer, *Am J Physiol* **45** 81 (Dec) 1917.

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- 8 Child, C M Am J Physiol **37** 219, 1915
- 9 Child, C M Senescence and Rejuvenescence, Chicago, 1915, pp 1-481
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- 31 Child, C M Biol Bull **45** 181, 1923
- 32 Child, C M, and Hyman, L H Biol Bull **36** 183, 1919
- 33 Hyman, L H J Exper Zool **20** 99, 1916
- 34 Hyman, L H Am J Physiol **40** 238, 1916
- 35 Hyman, L H J Exper Zool **24** 55, 1917
- 36 Hyman, L H Science **48** 518, 1918
- 37 Hyman, L H Am J Physiol **48** 340, 1919
- 38 Hyman, L H Am J Physiol **49** 377, 1919
- 39 Hyman, L H Am J Physiol **1** 67, 1919
- 40 Hyman, L H Biol Bull **37** 388, 1919
- 41 Hyman, L H Biol Bull **37** 404, 1919
- 42 Hyman, L H Am J Physiol **53** 399, 1920
- 43 Hyman, L H Biol Bull **38** 353, 1920
- 44 Hyman, L H Publ Puget Sd Biol Sta **2** 387, 1920
- 45 Hyman, L H Biol Bull **40** 32, 1921
- 46 Hyman, L H Proc Am Soc Zool, Anat Rec **24** 392, 1923
- 47 Hyman, L H J Exper Zool **37** 47, 1923
- 48 Hyman, L H, and Bellamy, A W Biol Bull **43** 313, 1922
- 49 Hyman, L H, and Galigher, A E J Exper Zool **34** 1, 1921
- 50 MacArthur, J W Am J Physiol **54** 138, 1920
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"Achlorhydria" denotes no free hydrochloric acid present at any stage before or during digestion, using dimethylamidoazobenzol and congo red as indicators. "Hypochlorhydria" denotes that the curve of free acid at no stage exceeded 0.036 per cent of hydrochloric acid. It will be observed that 44.4 per cent of gastric ulcers and 25 per cent of duodenal ulcers had either diminished or absent free hydrochloric acid. A recent series of Moynihan's,<sup>10</sup> similarly classified, showed corresponding percentages of 47.2 and 22.4. Four (14.8 per cent) of the gastric ulcer cases and one (15 per cent) case of duodenal ulcer had complete achlorhydria, Moynihan's corresponding percentages being 13.1 and 5.5.

Crispin,<sup>11</sup> in 1916, from the Mayo Clinic, recorded eleven cases of duodenal ulcer with achlorhydria. They were all proved by operation, but only a single one-hour examination of the gastric contents was made. Furthermore one case was associated with an empyema of the

*Cases of Gastric and Duodenal Ulcer Classified According to Their "Acid Curves"*

Type of Acid Curve	Gastric Ulcer		Duodenal Ulcer	
	Cases	Percentage	Cases	Percentage
Achlorhydria	4	14.8	1	2.5
Hypochlorhydria	3	11.1	0	0.0
Low normal	5	18.5	9	22.5
Normal	8	29.6	5	12.5
High normal	7	25.9	11	27.5
Hyperchlorhydria	0	0.0	14	35.0
Total	27		40	

gallbladder and three with gastric ulcers, these should be disregarded, for gallbladder disease itself is frequently associated with achlorhydria, as Crispin himself observes, and gastric ulcers more commonly than duodenal ulcer. The remaining six cases represent less than 1 per cent. of the total number of duodenal ulcers demonstrated at operation. Horner<sup>12</sup> in eight cases of gastric ulcer and fifteen of duodenal ulcers, proved at operation, found no case of anacidity, but this is a small series. Hardt<sup>13</sup> refers to a case of gastric ulcer with "typical" symptoms, in which repeated gastric analyses failed to find any free hydrochloric acid. He does not state, however, whether the ulcer was proved to exist. Hunter<sup>14</sup> examined twenty cases of ulcers of the body of the

10 Moynihan, B. Problems of Gastric and Duodenal Ulcer, Brit M J **1** 221 (Feb 10) 1923.

11 Crispin, E. L. Duodenal Ulcer, Interstate M J **23** 215 (March) 1916.

12 Horner, C. P. Fractional Test Meal, J A M A **69** 1931 (Dec 8) 1917.

13 Hardt, L. L. J. Studies of Cause of Pain in Gastric and Duodenal Ulcers, Peristalsis as Direct Cause of Pain in Gastric Ulcers with Achylia and in Duodenal Ulcers, Arch Int Med **29** 684 (May) 1922.

14 Hunter, D. Fractional Test Meal in Study of Disorders of Gastro-Intestinal Tract (Analysis of 174 Verified Cases), Quart J Med **16** 95 (Jan) 1923.

confirmed this fact by investigations on a human subject Moynihan<sup>5</sup> records his difficulty in convincing clinicians when "hyperacidity" or "acid dyspepsia" were such popular diagnoses that many of these cases were in fact cases of duodenal ulcer. He realized that many cases of duodenal ulcers occurred with diminished or normal stomach acidities. Gibson,<sup>6</sup> in 1911, showed in a series of proved cases that the acidity varied within wide limits.

In most instances, it is impossible to predict with any degree of certainty the state of the gastric acidity from a consideration of the symptoms alone. The results obtained by fractional gastric analysis have demonstrated that whereas duodenal ulcer is most frequently associated with an increased acidity, it is not uncommon to find low or normal acidities, thus confirming the views expressed by Moynihan and Gibson many years ago. Ascoli<sup>7</sup> states that hydrochloric acid may or may not be in excess in cases of duodenal ulcer, and if in excess the ulcers are usually recent. Gastric ulcer, on the other hand, is usually found to have diminished or even absent acidity. For this reason alone it is not always advisable to consider gastric and duodenal ulcer under the joint heading of peptic ulcer.

Cases are still recorded in which the actual presence of an ulcer is by no means certain. A diagnosis on clinical grounds alone, without positive roentgen-ray findings or actual demonstration of the ulcer by operation or postmortem, is not sufficiently reliable. This is especially true of gastric ulcer in which accurate clinical diagnosis is one of the greatest difficulty and uncertainty. The following series of gastric and duodenal ulcers consists of cases in which the ulcer had been seen either by roentgen-ray examination or at the time of operation. Of the twenty-seven cases of gastric ulcer, twenty-two had been demonstrated at operation and five seen as definite niches by roentgen-ray alone. Of the forty cases of duodenal ulcer, thirty-seven were proved by operation and three were seen by roentgen ray as persistent deformities of the duodenal cap. Adopting an arbitrary classification<sup>8</sup> based on a comparison between the curves of free acidity with the zone which included the curves of 80 per cent of normal persons examined by Bennett and Ryle,<sup>9</sup> the results shown in Table 1 were obtained.

5 Moynihan, B. G. A. *Diagnosis and Treatment of Duodenal Ulcer*. Lancet **1** 20 (Jan) 1910, *Some Points in Diagnosis and Treatment of Chronic Duodenal Ulcer*, *ibid*, **1** 9 (Jan) 1912.

6 Gibson, G. A. *Duodenal Ulcer Discussion*, Edinburgh M. J. **6** 325 (April) 1911.

7 Ascoli, V. *Ulcera duodenale*, *Riforma med* **38** 1093 (Nov 13) 1922.

8 Bell, J. R. *Consecutive Series of Four Hundred and Twenty-Five Gastric Analyses by Fractional Method*, *Guy's Hosp Rep* **72** 302 (July) 1922.

9 Bennett, T. I., and Ryle, J. A. *Study of Normal Gastric Function Based on Investigation of One Hundred Healthy Men by Means of Fractional Method of Gastric Analysis*, *Guy's Hosp Rep* **71** 286 (July) 1921.

to exist a diminished acidity is far more common than an increased acidity" Such provocative suggestions should stimulate the development of a more efficacious form of medical treatment of gastric ulcer

Some clinicians admit that a small percentage of patients with gastric ulcer have achlorhydria, but they consider that such cases do not present the same clinical symptoms as the "typical" gastric ulcer So far as gastric ulcer has any typical symptoms, no such distinction can be drawn from a study of the cases here recorded The first two cases described are representative of all

#### REPORT OF CASES

CASE 1—J W A, a man, aged 50, was admitted to the Leeds General Infirmary on Nov 30, 1922, complaining of pain in the epigastrium Until six years before, he had been perfectly well and free from indigestion, then pain in the upper epigastrium began to occur about one and a half hours after meals, and was relieved by taking food or sodium bicarbonate It continued on and off for three months, and then disappeared completely for some weeks Further similar attacks followed, and gradually the pain became an almost daily occurrence Six weeks before admission the pain became more severe and extended to both hypochondriac regions and through to the back, it was of a dull, aching character and usually accompanied by nausea Vomiting occurred on only three occasions with relief to the pain, the vomitus was sour tasting and burned his throat The pain never awakened him during the night He had always been very moderate in the use of alcohol and tobacco His appetite was unimpaired, but he had lost twelve pounds in weight in the past year Melena was never noticed, and no hematemesis occurred

*Examination*—The patient was well nourished and had good color The teeth and gums showed moderate pyorrhea The upper part of the abdomen was rigid, and tenderness in the midepigastrium was present on deep palpation Roentgen-ray examination showed a stomach of normal size with no delay in emptying A well marked persistent incisura was present high up near the esophageal opening, but there was no sign of a niche Fractional test meal showed complete achlorhydria with a total acidity not exceeding 0.05 per cent of hydrochloric acid (Chart 1) Operation (Nov 24, 1922) There was a chronic gastric ulcer on the posterior surface of the stomach, adherent to the pancreas, otherwise nothing abnormal was observed Partial gastrectomy and gastrojejunostomy were performed There was no evidence of malignancy on histologic examination

CASE 2—A E H, a woman, aged 60, was admitted to the hospital on Dec 1, 1922, complaining of attacks of pain in the epigastrium, which extended through to the back, for the last thirty-two years She had had no previous illnesses of significance The pain was frequently sharp and severe and came on about one hour after meals, but not regularly Intervals of complete freedom from pain, usually lasting several weeks, alternated with the attacks Twenty-three years before she had a severe melena and fainted, after which she was free from pain for seven years Seven years ago she had had some gallstones removed, but the pain persisted There had been no loss of appetite, and her weight had not altered greatly Nausea accompanied the pain but not vomiting

*Examination*—The patient had a fairly well nourished appearance Her teeth and gums were healthy There was no abdominal rigidity, but tenderness in the epigastrium and in a small area to the left of the tenth dorsal vertebra posteriorly was elicited A fractional test meal showed complete achlorhydria, with a total acidity not exceeding 0.077 per cent of hydrochloric acid (Chart 2)



stomach, all verified by operation or necropsy, by means of fractional gastric analysis. He found three (15 per cent) had complete achlorhydria. None of fifteen cases of duodenal ulcer, similarly verified, showed achlorhydria. It would therefore appear that gastric ulcer is associated with achlorhydria in a proportion of cases by no means negligible and that achlorhydria may occasionally accompany duodenal ulcer.

The experimental work of Bolton<sup>3</sup> and others afforded support to the hypothesis that the healing of a gastric ulcer is retarded by hyperacidity. Bolton also found, however, in a series of nineteen guinea-pigs in which he had produced ulcers, that there was a diminution in the acidity in the early stages, and a return to normal when healing had commenced. Hardt<sup>15</sup> concludes from his work on dogs that "there is no 'hyperacidity' in the gastric juice following the experimental production of gastric ulcers." There is no justification for the assumption that hyperacidity is necessarily one of the factors in the production of gastric ulcer.

Modern medical treatment of peptic ulcers seeks to achieve a cure by (1) neutralizing the acidity of the stomach contents as continuously as possible, and (2) administering a physically nonirritating and chemically non-acid-provoking diet. These principles are applied indiscriminately to both gastric and duodenal ulcer. Complete and rapid relief of pain (more rapid and effectual in the case of duodenal than of gastric ulcer) almost invariably results, but that this is due to the neutralizing effect of the alkali is by no means certain. At present, no method of medical treatment gives more satisfactory results when efficiently employed, although it is not always rational. Hardt and Rivers<sup>16</sup> directed attention to the harmful effects which may occasionally arise during intensive alkaline therapy, owing to the production of an alkalosis, and many clinicians have had similar experiences. If an achlorhydria is originally present, the danger of alkalosis resulting is all the greater, and neutralization by alkali is entirely 'irrational'. Smithies<sup>17</sup> puts forward the view that "when peptic ulcer exists, it is a matter of serious question whether the introduction into the stomach of sufficient alkali to neutralize hydrochloric acid is not injurious rather than beneficial," and Moynihan<sup>18</sup> pertinently asks "whether an 'acid' treatment of gastric ulcer would not be more rational than an 'alkaline' treatment" because "in cases in which a gastric ulcer has been proved

15 Hardt, L. L. J. Secretion of Gastric Juice in Cases of Gastric and Duodenal Ulcers, *Am J Physiol* **40** 314 (April) 1916.

16 Hardt, L. L., and Rivers, A. B. Toxic Manifestations Following Alkaline Treatment of Peptic Ulcer, *Arch Int Med* **31** 171 (Feb.) 1923.

17 Smithies, F. Significance of Etiologic Factors in Treatment of Peptic Ulcer, *J A M A* **74** 1555 (June 5) 1920.

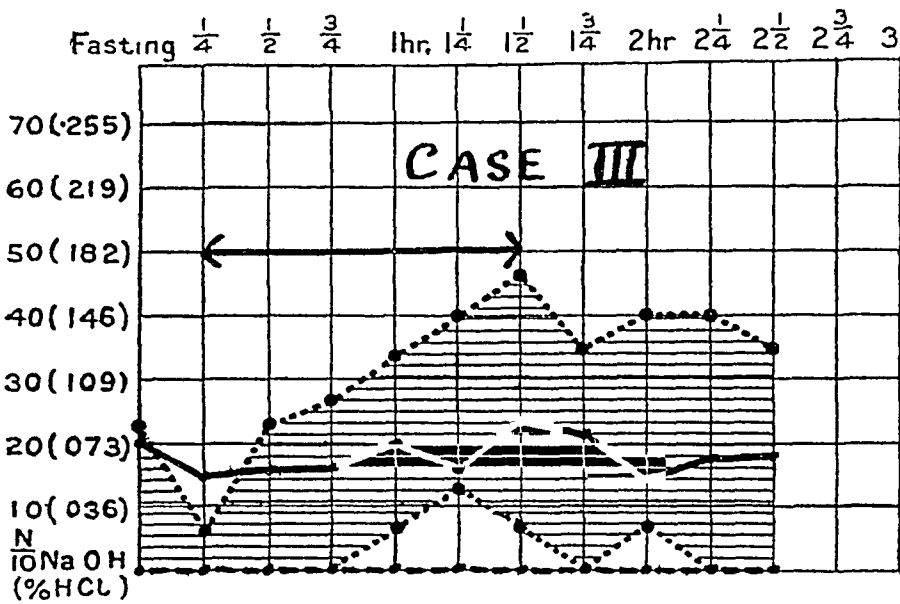


Chart 3—Results of fractional test meal in Case 3

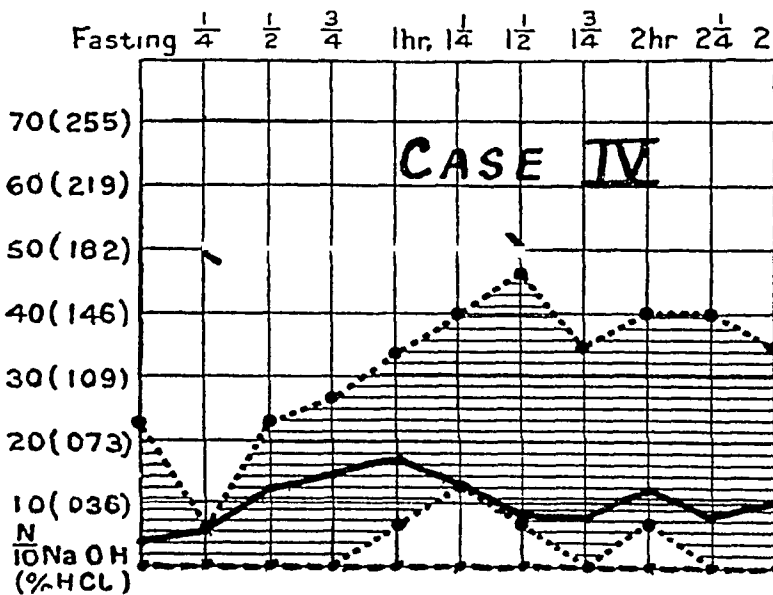


Chart 4—Results of fractional test meal in Case 4

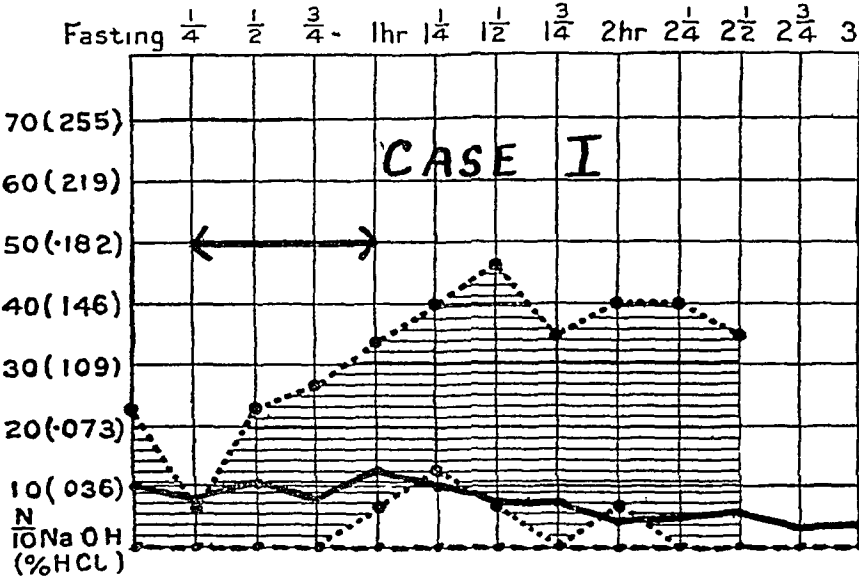


Chart 1—Results of fractional test meal in Case 1 The shaded area represents the limits of free hydrochloric acid (dimethyl indicator) for 80 per cent of normal people The dot and dash line represents free hydrochloric acid, the continuous line represents total acidity, the arrow line represents food present in the stomach

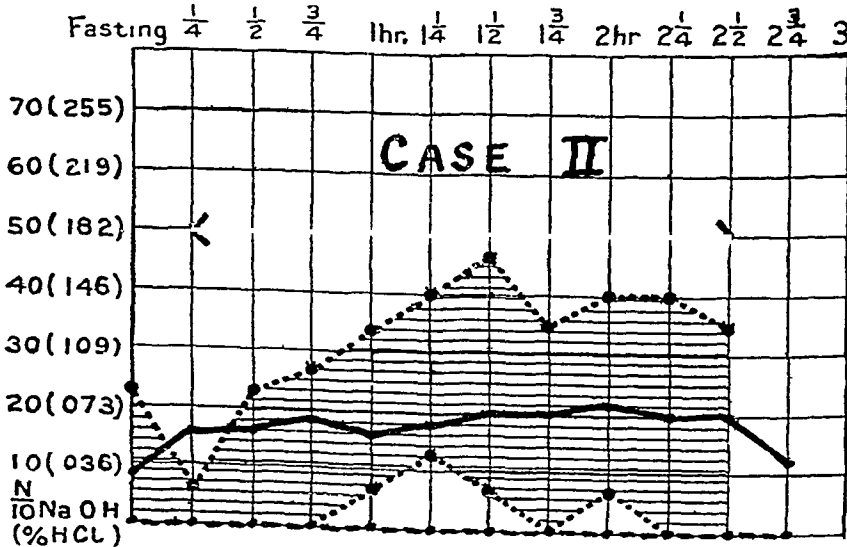


Chart 2—Results of fractional test meal in Case 2

Whether the achlorhydria preceded the development of the ulcer or resulted secondarily is uncertain, but from the point of view of treatment the important fact is its presence. The methods of medical treatment in general use are probably more efficient than those employed twenty years ago, but they still leave much to be desired. The secretory disturbances are so varied and diminished acidity so frequent in gastric ulcer that it is doubtful whether they play an important part in the failure of the ulcer to heal. Medical treatment of gastric ulcer must needs attain a higher level of efficiency, and this cannot obtain while irrational methods, founded on misconceptions, are deemed satisfactory.

#### SUMMARY

1 Twenty-seven proved cases of chronic gastric ulcer were examined by means of the fractional test meal. Four (14.8 per cent) had complete achlorhydria and three (11.1 per cent) had extremely low acidities.

2 Gastric ulcer is far more frequently associated with a diminished acidity than is duodenal ulcer, and it is exceptional to find complete achlorhydria with the latter.

3 These four cases of gastric ulcer were clinically indistinguishable from those associated with normal acidities. Neither the site nor the duration of the ulcer appeared to predispose to achlorhydria.

4 The methods in vogue in medical treatment of gastric ulcer, while producing many good results, are not wholly rational, and are based on misconceptions.

5 Recognition of the wide variations of secretory activity occurring in gastric and duodenal ulcer is essential for the efficient treatment of these conditions.

Operation (Dec 2, 1922) revealed dense adhesions everywhere and a small, very indurated gastric ulcer on the lesser curvature near the esophageal opening. The ulcer was cauterized, and posterior gastro-jejunostomy performed (Microscopically, there was no evidence of malignancy)

CASE 3—A fractional test meal given to E B, a woman, aged 54, revealed complete achlorhydria with a total acidity not exceeding 0.091 per cent of hydrochloric acid (Chart 3). Operation revealed definite pyloric obstruction. On the anterior wall of the pyloric antrum a chronic ulcer was found which was excised and a posterior gastro-jejunostomy performed. Otherwise nothing abnormal was observed. (There was no evidence of malignancy on histologic examination)

CASE 4—A fractional test meal given to A C, a woman, aged 51, showed complete achlorhydria, with a total acidity not exceeding 0.058 per cent of hydrochloric acid (Chart 4). Operation revealed a chronic ulcer about half way along the lesser curvature. No other abnormality was observed. Partial

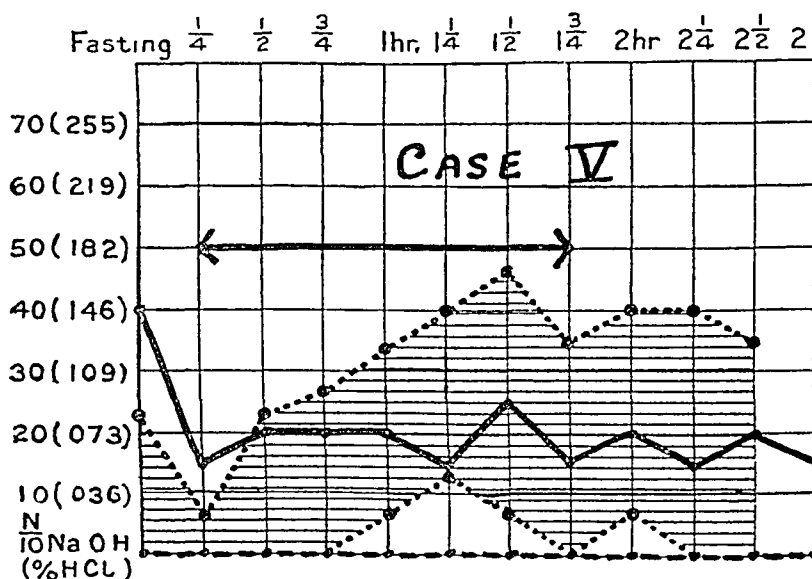


Chart 5—Results of fractional test meal in Case 5

gastrectomy and gastro-jejunostomy were performed. (Microscopically, there was no evidence of malignancy.)

CASE 5—A fractional test meal given to A S, a woman, aged 39, showed complete achlorhydria, with a total acidity not exceeding 0.146 per cent of hydrochloric acid (Chart 5). Operation revealed duodenal ulcer, but it was not dealt with, owing to an accompanying acute appendicitis for which appendicectomy was performed. (This patient had had a severe melena three years previously.)

#### COMMENT

A consideration of these cases shows that the achlorhydria is apparently not related to the situation or duration of the ulcer. They are indistinguishable clinically from ulcers associated with normal amounts of acid. Four of the five patients were females, and in this respect it is interesting to note that women tend to have lower gastric acidities than men as a general rule.

How far are these physiologic influences responsible for the changes in the duration of systole in man? Previous studies have indicated their possible operation in normal persons. A few such instances may be cited. Lombard and Cope<sup>4</sup> expressed the relation of systole length to rate by a formula, the constant of which varied with sex, posture, etc. They therefore suggested venous return as an added factor. Wiggers and Clough<sup>5</sup> found that while the duration of systole in normal persons followed a curve plotted on the duration of the cycle in a general way, there were many exceptions. They reported, in addition, a relative lengthening of systole in "irritable hearts" and suggested a myocardial factor as being responsible for this. The results of Bowen,<sup>6</sup> after exercise, indicate a lengthening of systole independent of heart rate changes. Finally, at rapid heart rates the duration of systole has been found to be shorter than Lombard and Cope's formula would indicate.<sup>7</sup>

As many cardiovascular affections are accompanied by changes in venous pressure and arterial resistance as well as abnormalities in the innervation and condition of the heart muscle—changes comparable to those experimentally produced in animals—it seemed advisable to determine whether the duration of systole and its phases in such clinical cases is also governed by these physiologic mechanisms. The present report deals with observations in auricular fibrillation. This condition was selected because in auricular fibrillation we obtained clinical cases with varying degrees of venous pressure and a large variation in the length of consecutive cycles, we find varying degrees of cardiac failure and varying amounts of heart muscle involvement, and, finally, there is an absence of synergic auricular contractions.

#### METHOD

In order to obtain the required data, heart sounds and the subclavian pulse were registered simultaneously by Frank segment capsules (Wiggers's<sup>8</sup> adaptation). A typical record from a normal person is illustrated in Chart 1. The records (plates) were measured by a Lucas comparator, and only those which permitted accurate reading were selected. The isometric contraction period was measured by a slight modification of the method of Wiggers and Clough<sup>5</sup>. In our work, it was computed by subtracting the time interval between the upstroke

4 Lombard, W. P., and Cope, O. M. *Proc Soc Exper Biol & Med* **16** 97, 1919, *Am J Physiol* **45** 564, 1918, *Ibid* **49** 139 and 150, 1919, *Ibid* **51** 474, 1920.

5 Wiggers, C. J., and Clough, H. D. *J Lab & Clin Med* **4** 644, 1919.

6 Bowen, W. D. *Am J Physiol* **11** 61, 1904.

7 Wiggers, C. J. Personal communication.

8 Wiggers, C. J. *Circulation in Health and Disease*, Ed 2, Philadelphia, Lea & Febiger, 1923, p. 180.

# CLINICAL OBSERVATIONS ON THE DYNAMICS OF VENTRICULAR SYSTOLE

## I AURICULAR FIBRILLATION \*

L N KATZ, M.D., AND H S FEIL, M.D.

CLEVELAND

According to recent physiologic investigations (Wiggers<sup>1</sup>), ventricular systole may be divided into a period of isometric contraction and a period of ejection, the latter being again divided into a phase of maximum and reduced ejection. Recent studies on animals<sup>2</sup> have, moreover, shown how the duration of these phases as well as the duration of the entire systole is modified by a number of dynamic factors<sup>3</sup>. In brief, while the duration of the average systole is determined by the heart rate or average cardiac cycle—or more precisely the duration of any systole is determined by the duration of the previous diastole—it is also affected by other experimentally produced dynamic changes, namely, the specific effect of the cardiac nerves, the action of chemicals, drugs and hormones, changes in arterial resistance, and alterations in venous pressure. The isometric contraction period, for instance, is shortened by an increase in venous pressure and by the action of epinephrin or carbon dioxide and lengthened slightly by an increase in arterial resistance. Again, the ejection phase is shortened by an abbreviation of the previous diastole, by an increase in arterial resistance (when unassociated with any pronounced systolic retention), by a decrease in venous pressure, by the specific action of the accelerator nerves, and by the action of epinephrin and carbon dioxide. It is lengthened by a prolongation of the previous diastole, and by an increase in venous pressure (whether the result of an increased venous return or the back pressure effect of an increased systolic retention). Of the two phases, ejection is the more variable. In fact, the changes in the duration of systole are largely determined by the duration of the ejection phase. As a result, it was concluded that the duration of these phases depends on (a) the initial tension and diastolic volume of the ventricle, (b) the arterial resistance, and (c) the condition of the heart muscle.

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\* From the Medical Clinic of Western Reserve University at City Hospital

1 Wiggers, C J. *Am J Physiol* **56** 415, 1921

2 Wiggers, C J, and Katz, L N. *Am J Physiol* **53** 49, 1920. Katz, L N. *J Lab & Clin Med* **6** 291, 1921. Wiggers, C J. *Am J Physiol* **56** 439, 1921.

3 Wiggers, C J, and Katz, L N. *Am J Physiol* **58** 439, 1922

3 The literature on this subject is reviewed in these reports

## DURATION OF SYSTOLE AND ITS PHASES IN NORMAL PERSONS

In studying the possible factors modifying the duration of systole and its phases in cases of auricular fibrillation, it is obviously necessary to compare them with normal subjects. Although the relation of systole length to heart rate, cycle length, etc., has been repeatedly investigated, it seemed desirable to test a small series of normal persons by our methods in order to be quite certain that they checked with those of previous observers. The data so obtained from fifteen normal adults, ranging in age from 20 to 30 years, is arranged in Table 1 according to the duration of the average cardiac cycle (Column III). This gives a range of cycle length from about 0.59 of a second, in Case 1, to 0.183 of a second in Case 15, comparable to heart rates ranging from 100 to 54 per minute (Column IV). In Column V is shown the duration of the previous diastole, and a little computation shows that this period increases with the cycle length, but not proportionately. This is due to the fact, shown in Column VI, that the duration of total systole also tends to increase as the cycle lengthens. In Columns VII and VIII are given the figures for the duration of the isometric contraction and ejection phases. A study of these figures shows a great variability in the duration of the isometric phase, a variability entirely independent of the duration of the cycle, previous diastole, total systole or ejection phase. The ejection phase, on the other hand, becomes longer, with but few exceptions, as the cycle lengthens.

Such relations show that in man, as in animals, the influence of heart rate or cycle length on the duration of systolic ejection is determined chiefly through the variation in the duration of diastolic filling, the ejection period progressively lengthening with longer diastoles, due to the greater amount of blood to be ejected in these beats.

The formula  $S = 0.31 \sqrt{C}$ , for the recumbent position, which was evolved by one of us<sup>3</sup> from the formula  $S = \frac{60}{K/R}$  of Lombard and Cope,<sup>4</sup> was tested in our series by calculating a theoretical "systole" ( $S$ ) from the average cycle length ( $C$ ) and comparing it with the average systole and ejection for that individual. The values for ( $S$ ) which are given in Column IX, of Table 1, are shorter than the average total systole, except in Cases 6, 14, and 15 of this series (compare Column IX with VI). They are somewhat longer than the corresponding ejection period (compare Column IX with VIII). The results on the whole agree within limits with those of Lombard and Cope, for it should be remembered that their constant was used to measure ejection plus protodiastole (that is, upstroke to bottom of incisura of the carotid pulse) and not total systole. We should therefore compare the calculated  $S$  with ejection rather than with total



of the subclavian pulse and the bottom of the incisura (Fig 1, *a* to *c*) from the interval between the first and second sounds (Fig 1, I to II) Ejection was readily computed from the subclavian pulse by the time interval between the upstroke and the beginning of the incisura (Fig 1, *a* to *b*) The duration of diastole was obtained by subtracting the sum of the ejection and isometric periods, as determined above, from the interval between two successive second heart sounds (Fig 1, II<sup>1</sup> to II) The latter was our criterion of cycle length, while the sum of ejection and isometric periods gave the duration of the total systole In studying the effect of heart rate on systole, it was obviously preferable to use the preceding diastole rather than the succeeding one, as has been pointed out elsewhere<sup>9</sup>

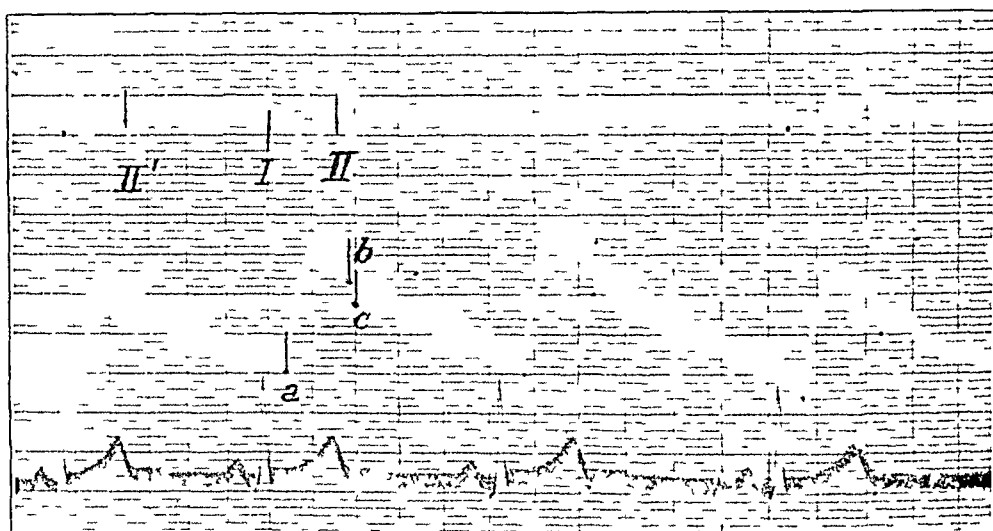


Fig 1—Simultaneous record of heart sounds (top curve), subclavian arterial pulse (middle curve), and electrocardiogram, Lead II (bottom curve) of normal person I, beginning of first heart sound, II, II', this and the succeeding illustrations have been reduced two thirds, beginning of second heart sound, *a*, beginning of ejection, *b*, sharp drop of incisura, *c*, bottom of incisura Time in this and succeeding records is 0.2 of a second

The records were obtained from ward patients The diagnosis of auricular fibrillation was confirmed electrocardiographically The cases were classified according to probable etiology into those with mitral valvulitis and those with myocardial fibrosis (or so-called chronic myocardiitis) The absence or presence of cardiac failure was noted and, when present, the degree of failure ascertained The nature and amount of therapy preceding the taking of the records and the blood pressure estimation at the time were also noted Records were taken with the patient in the recumbent position and in most cases with respiration arrested

TABLE 1—*Duration of Systole and Its Phases in Normal Persons*

I Case	II Number of Beats Measured	III Duration of Cycle		IV Heart Rate		V Duration of Previous Diastole		VI Duration of Total Systole		VII Duration of Isometric Contraction Period		VIII Duration of Systolic Ejection Phase		IX Calculated Systole From Formula $S = 0.31\sqrt{C}$
		Average	Deviation From Average	Average	Deviation From Average	Average	Deviation From Average	Average	Deviation From Average	Average	Deviation From Average	Average	Deviation From Average	
1 M B *	5	0.538	+0.010 -0.008	100	+0.010 -0.011	0.308	+0.010 -0.011	0.290	+0.003 -0.001	0.063	+0.002 -0.003	0.252	+0.002 -0.002	0.239
2 Ad	5	0.753	+0.081 -0.025	80	+0.082 -0.031	0.471	+0.082 -0.031	0.282	+0.008 -0.006	0.040	+0.006 -0.003	0.242	+0.004 -0.005	0.269
3 We	4	0.760	+0.017 -0.008	79	+0.024 -0.015	0.460	+0.024 -0.015	0.300	+0.007 -0.007	0.053	+0.007 -0.007	0.247	+0.011 -0.003	0.270
4 Al	3	0.771	+0.033 -0.044	78	+0.030 -0.011	0.464	+0.030 -0.011	0.307	+0.003 -0.003	0.063	+0.001 -0.001	0.244	+0.002 -0.003	0.272
5 Ma	3	0.792	+0.036 -0.026	76	+0.044 -0.025	0.491	+0.044 -0.025	0.298	+0.003 -0.003	0.031	+0.002 -0.002	0.267	+0.005 -0.001	0.276
6 Kel	6	0.804	+0.030 -0.061	75	+0.025 -0.059	0.538	+0.025 -0.059	0.260	+0.004 -0.004	0.037	+0.002 -0.002	0.259	+0.003 -0.007	0.278
7 Kele	6	0.809	+0.033 -0.012	74	+0.028 -0.018	0.512	+0.028 -0.018	0.297	+0.006 -0.007	0.000	+0.003 -0.004	0.237	+0.006 -0.003	0.279
8 J W	3	0.827	+0.019 -0.017	73	+0.023 -0.023	0.525	+0.023 -0.023	0.302	+0.003 -0.003	0.029	+0.004 -0.005	0.272	+0.002 -0.003	0.282
9 A S	4	0.869	+0.017 -0.012	70	+0.018 -0.024	0.515	+0.018 -0.024	0.354	+0.014 -0.008	0.087	+0.002 -0.003	0.267	+0.014 -0.008	0.289
10 J P	12	0.878	+0.078 -0.049	68	+0.076 -0.039	0.539	+0.076 -0.039	0.339	+0.014 -0.014	0.056	+0.005 -0.004	0.283	+0.013 -0.011	0.291
11 Fr	7	0.924	+0.010 -0.023	65	+0.014 -0.021	0.601	+0.014 -0.021	0.323	+0.005 -0.004	0.048	+0.006 -0.005	0.275	+0.002 -0.005	0.298
12 A Se	3	0.934	+0.166 -0.186	64	+0.171 -0.195	0.625	+0.171 -0.195	0.309	+0.005 -0.013	0.034	+0.008 -0.006	0.275	+0.015 -0.012	0.300
13 We	8	1.011	+0.088 -0.046	59	+0.093 -0.073	0.646	+0.093 -0.073	0.360	+0.009 -0.011	0.078	+0.008 -0.008	0.287	+0.011 -0.013	0.312
14 R W †	4	1.087	+0.071 -0.063	55	+0.028 -0.052	0.778	+0.028 -0.052	0.309	+0.010 -0.021	0.050	+0.007 -0.011	0.259	+0.006 -0.004	0.323
15 At S ‡	3	1.107	+0.076 -0.044	54	+0.053 -0.017	0.798	+0.053 -0.017	0.309	+0.005 -0.007	0.036	+0.006 -0.005	0.273	+0.006 -0.003	0.326

\* Indicates female (all others male), Q-R-S-T interval 0.308 sec (+0.008 to -0.007)

† Q-R-S-T interval 0.429 sec (+0.008 to -0.007)

‡ Q-R-S-T interval, 0.429 sec (+0.002 to -0.004)

The interval of time given is the average, the plus and minus figure represents the maximum and minimum deviation from this

systole It will be seen in Table 1 that the calculated  $S$  is actually greater than the ejection phase by a time interval varying from 0.008 to 0.064 of a second, or on the average 0.028 of a second, which is reasonably equivalent to the duration of protodiastole in man, as found by Burstein<sup>10</sup>

In considering the variations of the phases of consecutive beats in one person, we find that diastole is always more variable than systole and that the systolic ejection, as a rule, varies more than the isometric period Thus in Case 10, Table 1, in which twelve consecutive beats were measured, the duration of the previous diastole varies from the average by plus 0.076 and minus 0.039 of a second, while total systole varies from the average by plus 0.014 and minus 0.014 of a second (Columns V and VI) In the same case the variations from the average are plus 0.013 and minus 0.011 of a second for the ejection

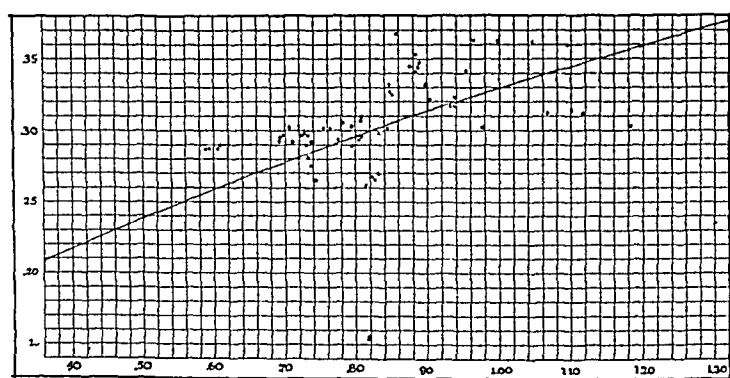


Fig 2—Plot showing the relation of total systole to corresponding cycle length in fifteen normal cases, and related to curve drawn from the formula  $S = 0.31 \sqrt{C}$

phase as compared with plus 0.005 and minus 0.004 of a second for the isometric period (Columns VII and VIII) A like consideration of other cases in the table will show similar relationships

On plotting the relation of systole to cycle length according to the method of Wiggers and Clough,<sup>5</sup> as in Figure 2, it was found that although there was a definite relation between the individual systole and the corresponding cycle length, there were, however, occasional exceptions These were no doubt due to the factors already referred to in the preliminary discussion, the result of such influences as respiration, change in the tonus of the cardiac nerves, etc

Our findings, then, in normal persons are in accord with those of Lombard and Cope in a general way, and agree closely with the results of Wiggers and Clough It may therefore be concluded that rate for

rate the phases of systole in normal persons compare with those obtained from the experimental observations of Wiggers and Katz, and that the changes in their duration follow the same laws

#### DURATION OF SYSTOLE AND ITS PHASES IN AURICULAR FIBRILLATION

*Comparison with Normal*—The data of sixteen series of observations on fifteen patients with auricular fibrillation are tabulated in Table 2. As this table shows, the patients were adults varying in age from 30 to 72 years (Column V), with blood pressures (maximum systolic—minimum diastolic) ranging from systolic, 210, diastolic, 120, to systolic, 100, diastolic, 68 (Column IV). This series included seven cases with an associated myocardial fibrosis or so-called chronic myocarditis (*My F*) and eight with an associated mitral valvulitis (*MS*) (Column VI). Seven of the patients had not received any of the digitalis group of drugs (indicated by *O* in Column VII) while nine were "digitalized" to a variable degree when the records were obtained (*Dig* in Column VII). Two of the latter had received some quinidin sulphate in addition (*Quin* in Column VII). Three of the patients showed no evidence of cardiac failure at the time the record was taken (indicated by — in Column VIII), seven had signs of partial or moderate cardiac failure ( $\pm$  and  $+$  in Column VIII), and the other six exhibited evidence of marked failure ( $++$  and  $+++$  in Column VIII).

This table is also arranged according to the duration of the average cardiac cycle (Column IX). It gives a range of cycle lengths varying from 0.172 of a second in Case 1, to 1.72 of a second in Case 16, with a variation in predominant rate ranging from 186 to forty-six beats per minute (Column III). A careful analysis of this table shows that, as in the normal controls, the average diastole (Column X) lengthens with a lengthening of the cycle (Column IX), but not proportionately, the disproportion being due to the simultaneous lengthening of the average total systole (Column XI). Again as in normal cases, the duration of the average isometric contraction period (Column XII) varies independently of the other phases and of the predominant rate, whereas the average systolic ejection phase (Column XIII) in general changes directly with the cycle length and largely determines the duration of total systole.

A comparison of this table with Table 1 brings out some further interesting facts. Not only is the range of cycle lengths greater than normal in the series of auricular fibrillation cases, but the deviation from the average in a single case is also greater. This is also true of the duration of diastole and the isometric and ejection phases. Total systole, although deviating but little more from the average than normal, is surprisingly constant in a person with fibrillation, considering the greater variation of previous diastole. For example, Case 5, Table 2,

TABLE 2—Duration of Systole and Its Phases in Atrial Fibrillation

I	Case	II Number of Beats Mea- sured	III Predom- inant Heart Rite	IV Maxi- mum Systolic and Mini- mum Diastolic Blood Pressure	V Age	VI Diag- nosis	VII Car- diac Medi- cation	VIII Degree of Cardiac Failure	IX Duration of Cycle		X Duration of Preceding Diastole		XI Duration of Total Systole		XII Duration of Isometric Con- traction Period		XIII Duration of Systolic Eje- ction Phase		XIV Calcu- lated From Formula $S=0.41\sqrt{G}$
									Aver- age	Devia- tion From Aver- age	Aver- age	Devia- tion From Aver- age	Aver- age	Devia- tion From Aver- age	Aver- age	Devia- tion From Aver- age	Aver- age	Devia- tion From Aver- age	
1	A F <sub>1</sub>	34	186	128/85	68	My F	Dig	++	0.323	+0.151 -0.158	0.200	+0.181 -0.087	0.123	+0.026 -0.027	0.037	+0.027 -0.022	0.086	+0.031 -0.031	0.176
2	O Sp	22	151	124/80	57	M S	0	++	0.397	+0.190 -0.144	0.222	+0.188 -0.098	0.175	+0.017 -0.042	0.047	+0.041 -0.038	0.128	+0.029 -0.036	0.195
3	R T <sub>1</sub>	5	127	162/104	65	My F	0	—	0.470	+0.075 -0.078	0.175	+0.067 -0.030	0.275	+0.029 -0.028	0.081	+0.014 -0.019	0.194	+0.021 -0.019	0.213
4	H L <sub>1</sub>	7	114	210/120	72	My F	Dig	++	0.525	+0.120 -0.180	0.302	+0.072 -0.119	0.223	+0.020 -0.028	0.062	+0.019 -0.011	0.161	+0.024 -0.044	0.225
5	H Lea *	13	111	145/90	45	M S	0	—	0.540	+0.113 -0.119	0.307	+0.106 -0.118	0.233	+0.026 -0.023	0.036	+0.037 -0.021	0.194	+0.021 -0.049	0.226
6	M Sh	8	110	170/?	61	My F	Dig Quin	++	0.545	+0.377 -0.137	0.323	+0.354 -0.131	0.222	+0.023 -0.019	0.058	+0.025 -0.028	0.163	+0.037 -0.033	0.229
7	M Gu	5	98	162/80	70	My F	Dig	±	0.610	+0.209 -0.148	0.331	+0.211 -0.114	0.279	+0.015 -0.016	0.073	+0.018 -0.018	0.206	+0.030 -0.022	0.242
8	D D <sub>1</sub>	6	96	140/80	47	M S	0	±	0.625	+0.047 -0.056	0.374	+0.030 -0.032	0.271	+0.031 -0.016	0.069	+0.021 -0.010	0.182	+0.022 -0.025	0.245
9	J Kot 11/16/22	15	94	110/90	36	M S	0	±	0.637	+0.151 -0.169	0.351	+0.161 -0.128	0.266	+0.037 -0.021	0.063	+0.037 -0.028	0.173	+0.037 -0.063	0.247
10	J Kot 7/2/22	12	93	110/90	36	M S	Dig	+	0.640	+0.289 -0.232	0.398	+0.264 -0.223	0.242	+0.043 -0.033	0.061	+0.072 -0.035	0.181	+0.063 -0.081	0.248
11	V Kr	25	90	120/86	30	M S	0	—	0.664	+0.419 -0.172	0.420	+0.407 -0.131	0.244	+0.034 -0.038	0.044	+0.032 -0.020	0.200	+0.030 -0.032	0.252
12	Jo Ber	9	76	132/80	40	M S	Dig	+++	0.787	+0.166 -0.062	0.478	+0.132 -0.036	0.369	+0.014 -0.015	0.119	+0.033 -0.025	0.199	+0.019 -0.019	0.275
13	Ju Ben	8	70	110/60	56	My F	Dig Quin	+	0.860	+0.144 -0.112	0.600	+0.141 -0.117	0.260	+0.018 -0.016	0.030	+0.015 -0.017	0.230	+0.008 -0.010	0.288
14	G G <sub>1</sub> *	10	69	100/68	44	M S	Dig	+	0.872	+0.210 -0.191	0.618	+0.228 -0.217	0.254	+0.020 -0.029	0.076	+0.031 -0.026	0.198	+0.027 -0.035	0.290
15	M St	6	55	125/90	34	M S	Dig	+	1.079	+0.478 -0.236	0.749	+0.467 -0.231	0.330	+0.011 -0.016	0.069	+0.012 -0.021	0.261	+0.032 -0.022	0.322
16	A W <sub>1</sub>	6	46	160/100	50	My F	0	++	1.295	+0.277 -0.425	0.910	+0.272 -0.118	0.355	+0.015 -0.021	0.091	+0.012 -0.011	0.264	+0.007 -0.010	0.352

— indicates no cardiac failure. +, moderate cardiac failure. ++ and +++ marked cardiac failure. M S, mitral valvulitis (infectious origin). My F, myocardial failure (40 ealed chronic myocardiitis). Dig, patient more or less digitalized (at time or just before record taken). Quin, quinidin.

systoles in this figure are shorter and are closer to the line of calculated "systole"—cycle ratios (computed from the formula  $S = 0.31/\sqrt{C}$ ) than in Figure 2, the plot of the normal cases. Similar plotting of all the ejection phases showed an even greater difference between normal and fibrillation records.

What is the cause of this shortening? A survey of the variables given in Table 2 demonstrates that the shortening of ejection is unrelated to most of them. It is not related to the age of the patient, to the height of the blood pressure nor to the associated cardiac condition. It occurs in like degree in patients who have been "digitalized" and those who have not. The only condition that seems to modify it is the degree of cardiac failure.

*Relation of Cardiac Failure to Duration of Systole and Ejection in Auricular Fibrillation—Anticipated Results*—It is apparent that cardiac failure increases the venous pressure because a relatively greater volume of blood is retained on the venous side—and with this the arterial pressure may be unchanged or even relatively reduced. We may anticipate then, *a priori*, that the increase in venous pressure and the lowering of the arterial pressure, when present, together with the slower rate of contraction of the diseased or fatigued heart, would lengthen the systole and its phases, and that this lengthening would vary directly with the degree of cardiac failure.

*Actual Results*—Contrary to our expectations, and much to our surprise, the actual results (as shown above) are just the reverse. The duration of ejection seems to be inversely proportional to the degree of cardiac failure, that is, the length of systole, and particularly ejection, varies on the whole inversely with the degree of failure. For example, cases with no evidence of cardiac failure, Cases 3, 5 and 11, of Table 2, show a difference between calculated  $S$  and the average ejection of 0.019, 0.034 and 0.053 of a second, respectively (Column XIV minus Column XIII), an average difference of 0.035 of a second, while cases with marked cardiac failure, Cases 1, 2, 4, 6, 12 and 16, have respectively a difference of 0.09, 0.067, 0.064, 0.066, 0.085 and 0.088 of a second, or an average difference (0.076 of a second) more than twice that of the preceding cases. The cases with partial failure, Cases 7, 8, 9, 10, 13, 14 and 15 have differences between the other two, the differences being respectively 0.036, 0.063, 0.074, 0.067, 0.058, 0.092 and 0.061 of a second, an average difference of 0.064 of a second.

*Discussion*—How can this discrepancy between anticipated and actual results be accounted for? Several explanations may be hazarded. For instance, an alteration in the blood chemistry associated with a deficient circulation might so change the condition of the heart as to make it contract for a shorter interval. Again, the pathologic condition

shows that with a variation of plus 0.113 and minus 0.119 of a second from the average cycle length (Column IX) and of plus 0.106 and minus 0.118 from the average diastole (Column X), the isometric contraction phase deviates from the average by only plus 0.057 and minus 0.021 of a second (Column XII), the systolic ejection by plus 0.021 and minus 0.049 of a second (Column XIII), and the total systole by plus 0.026 and minus 0.023 of a second

*Shortening of Systole and Its Ejection in Auricular Fibrillation*—A like comparison of averages shows the average isometric periods to be slightly longer in persons with auricular fibrillation than in normal persons (compare Column XII, Table 2, with Column VII, Table 1) Much more striking is the fact that the average total systoles and particularly the average ejection phases are shorter than normal at corre-

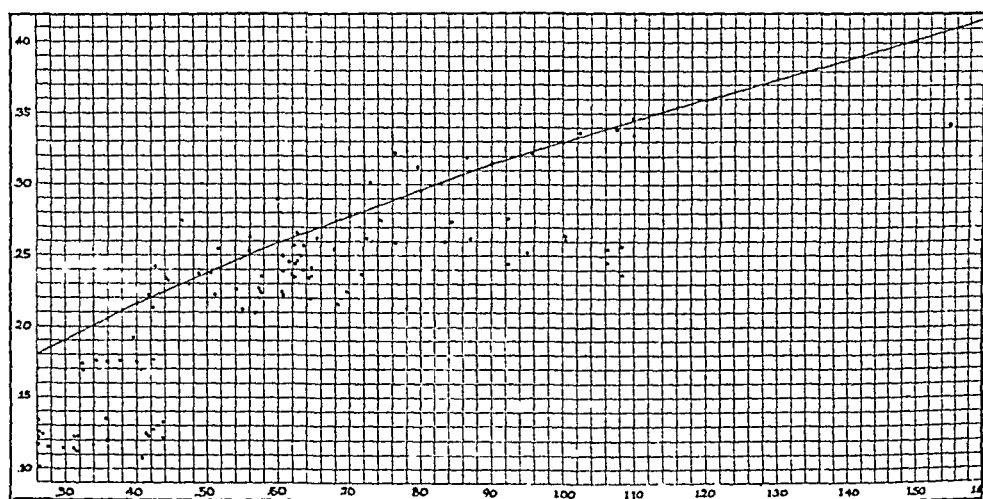


Fig 3—Plot showing the relation of total systole to corresponding cycle length in sixteen series of observations in fifteen cases of clinical fibrillation of the auricles, and related to curve drawn from the formula  $S = 0.31 \sqrt{C}$

sponding rates (compare Column XI and Column XIII, Table 2, with Column VI and Column VIII, Table 1)

This relative shortening is shown in another way, namely, by comparing the average ejection phase with  $S$  calculated (as pointed out above) for the corresponding average cycle length which is given in Column XIV. A little computation shows the average ejection phase in auricular fibrillation is from 0.019 to 0.092 of a second shorter than  $S$ , the average difference being 0.07 of a second. This is a considerably greater shortening than obtains in the normal series, the difference in the latter being, on the average only 0.028 of a second (as already mentioned). That this shortening of systole holds not only for average beats but also for individual beats is shown by plotting all systoles according to cycle length (Fig 3). It is obvious that the individual

electrocardiographically Figure 4 presents the electrocardiogram, Lead II, taken during auricular fibrillation and Figure 5 during normal mechanism The two sets of observations were taken two days apart Twenty-two beats were measured on each occasion

The average durations (and deviation from the average) are tabulated in Table 3 Analysis of this table shows a slightly more rapid predominant rate during fibrillation than when the mechanism was normal Ejection and systole shorten more than can be accounted for by

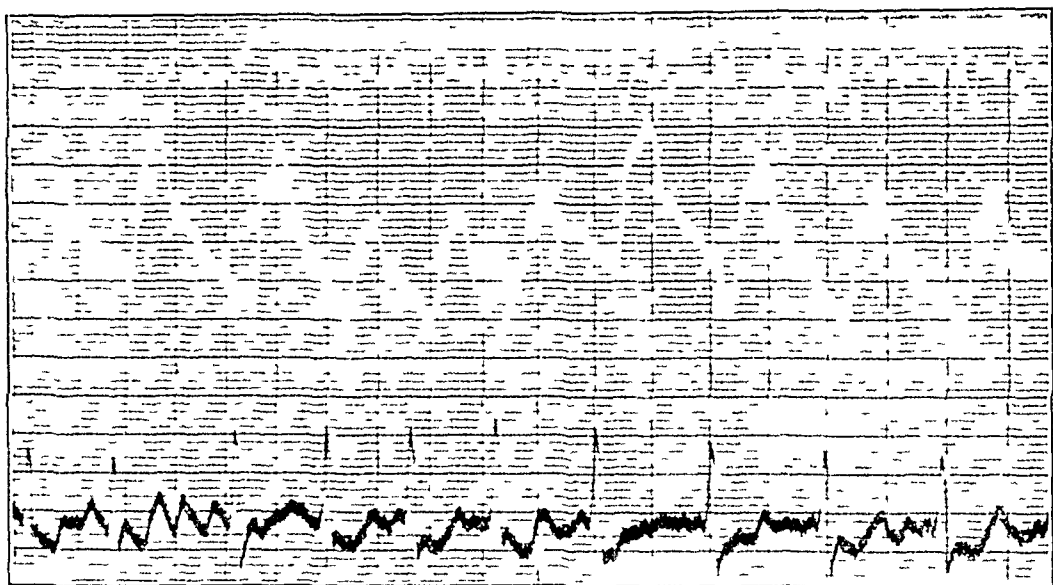


Fig 4—Simultaneous record of heart sounds (top curve), subclavian arterial pulse (middle curve), and electrocardiogram, Lead II, (bottom curve) of a case of paroxysmal auricular fibrillation during a period of fibrillation

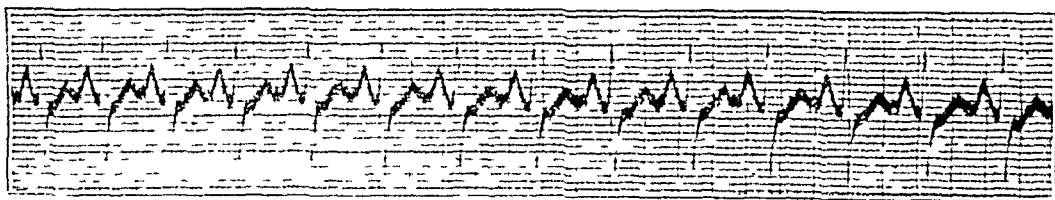


Fig 5—Electrocardiogram, Lead II, from patient illustrated in Figure 4, during normal mechanism

this slight change in rate According to the calculated  $S$ , "systole" should be 0.015 of a second shorter during the fibrillation than during the period of normal mechanism, whereas in reality the shortening of the average ejection is 0.043 of a second and that of the average total systole is 0.051 of a second When the auricular contractions are present, the average ejection phase is 0.039 of a second less than the corresponding calculated  $S$ , while the difference is almost twice as great (0.067 of a second) when the synergic auricular contractions are absent If the change in duration of ejection is compared with the change in



of the myocardium might alter its response to the progressive increase in venous pressure. Thus, we may suppose that the increase in venous pressure which in the early stages of failure is a compensatory mechanism becomes a detrimental factor as failure progresses, for we know that the inefficient (exhausted) heart fails to respond to the progressive increase of venous pressure and does not empty its contents completely.<sup>11</sup> Perhaps the duration of ejection reverses in a similar manner. There is, however, still another possible explanation.

*Relation of Duration of Systole and Its Ejection to the Absence of Synergic Auricular Contraction in Fibrillation of the Auricles*—It is possible that this discrepancy between anticipated and actual results is peculiar to auricular fibrillation and does not occur when the mechanism is normal. Auricular fibrillation is characterized among other things by an absence of synergic auricular contractions, and this may be the cause of the shortening of ejection. Auricular systole has been found to contribute a variable but measurable amount of blood to the ventricles. Wiggers and Katz,<sup>2</sup> for example, recently found the auricular contribution to vary from 18 per cent to 60 per cent of the total filling in normal dogs. In auricular fibrillation the absence of this portion of the contribution and the consequent lessened filling would cause a relative shortening of systole and its ejection phase because of the relatively lower initial tension.

The validity of this hypothesis can best be tested in man in cases of paroxysmal auricular fibrillation. For in this condition there is a spontaneous alteration of mechanism within a short period of time which permits a comparison of the duration of systole and its ejection phase during both mechanisms in a single person under otherwise practically constant conditions. The patient in Case 2 of Table 2 happened to be such a person. In this patient auricular fibrillation would develop spontaneously, last a variable time (a few hours to several days) and then spontaneously revert to a normal mechanism. Fortunately for us, the heart rate remained rapid throughout, so that the changes in the duration of systole and its ejection phase, which were found, were not due to a change in heart rate. They could, therefore, be attributed to the absence of synergic auricular contractions. The paroxysms occurred many times during her stay in the hospital and even while she was receiving large quantities of digitalis, as well as during the time she was receiving quinidin sulphate. The patient had signs of marked cardiac failure and died a short time after the records were taken. The diagnosis of paroxysmal auricular fibrillation was of course confirmed

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11 Wiggers, C. J., and Katz, L. N. *Am J Physiol* **58** 439, 1922. Patterson, S. W., and Starling, E. H. *J Physiol* **48** 357, 1914. Patterson, Piper, and Starling. *J Physiol* **48** 465, 1914.

of the heart or circulation. In general a lengthening of diastole causes an almost proportional lengthening of the following ejection period and an almost proportional shortening of the isometric period, whereas a shortening of diastole has the opposite effect. Total systole varies in the same direction as the ejection phase, but because of the opposite

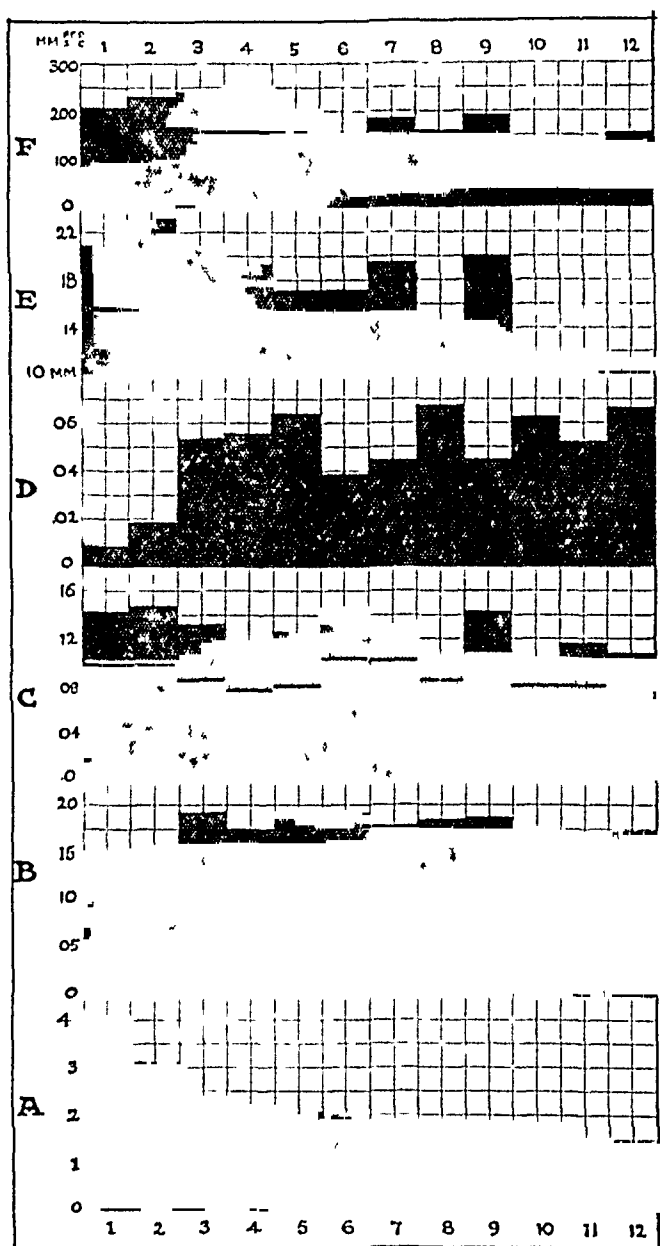


Fig. 6—Relation of the dynamics of systole to diastole

change in the isometric period, to a lesser degree. There are, however, many exceptions to all of these relationships. A typical Case is graphically illustrated in Figure 6 compiled from Case 10, Table 2. The twelve beats of this series are arranged according to the duration of diastole, starting with the longest and ending with the shortest (Fig. 6, A). Figure 6, B represents the duration of the corresponding suc-

the length of the preceding diastole, the discrepancy is even greater, as is also the case when a tabulation of all the beats is analyzed (Fig 3)

This case, therefore, shows that the absence of synergic auricular contraction causes in itself a relative shortening of systole and ejection. Indeed the progressive shortening with cardiac failure found in this series (Table 2) may be attributed to the greater susceptibility of the inefficient heart to slight changes in initial tension. Thus, on this assumption it can be argued that the decrease in filling produced by the absence of auricular contraction elicits a relatively greater response (shortening of ejection time) in the failing heart than in the efficient one, and that this response (shortening) is proportional to the degree of cardiac failure. At the present time, this appears to be the most logical explanation. Observations of other clinical conditions and on

TABLE 3—Average Duration of Systole and Deviations from the Average in a Case of Paroxysmal Auricular Fibrillation

I	II	III	IV	V	VI	VII
Cardiac Mechanism	Predom inant Rate	Duration of Cycle	Duration of Preceding Diastole	Duration of Total Systole	Duration of Systolic Ejection	Duration of Systole as Anticipated From Formula $S = 0.31\sqrt{C}$
Auricular fibrillation	151	+0 155 0 397 sec -0 076	+0 180 0 222 sec -0 075	+0 013 0 175 sec -0 024	+0 017 0 128 sec -0 021	0 195 sec
Normal	130	+0 018 0 460 sec -0 016	+0 025 0 234 sec -0 010	+0 012 0 226 sec -0 015	+0 014 0 171 sec -0 010	0 210 sec
Difference	21	0 063 sec	0 012 sec	0 051 sec	0 043 sec	0 015 sec

animals are, however, contemplated to further test the validity of this hypothesis

#### THE DYNAMIC INFLUENCE OF THE CONSTANTLY CHANGING CYCLE LENGTH IN AURICULAR FIBRILLATION

*Effect on the Duration of Systole and Its Phases in Successive Beats*—Changing heart rate in normal animals has been found to alter not only the duration of systole and its phases, but also the systolic discharge and velocity of ejection.<sup>12</sup> It is therefore interesting to see if this is also true in man. The constantly changing rate in auricular fibrillation gives an opportunity to determine this.

An analysis of our results demonstrates that the duration of the systolic phases alters from beat to beat with changes in cycle length. Indeed the response is practically the same regardless of the condition

12 Henderson, Y, and Associates. Am J Physiol **16** 325, 1906, *ibid* **31** 288, 352, 1913. Straub, H. Deutsch Arch f klin Med **115** 531, 1914, *ibid* **118** 214, 1915. Also Footnote 11.

Figure 6 illustrates these findings graphically. Figure 6, *E* represents the height of the individual pulse beats (in millimeters) in the case already referred to. When this is compared with the duration of the preceding diastole (Fig 6, *A*) we find that the height of the beat on the whole decreases as the diastole shortens, although there are many deviations, and that this shortening is proportionately greater in the beats with the shorter diastoles.

Do these changes in pulse size indicate like changes in systolic discharge? According to Frank<sup>14</sup> the arterial pressure (and with it the pulse) is the result of two variable factors—the rate of ejection from the ventricle and the peripheral flow from the arterial system. The peak of the pulse curve marks the point at which the two are equal. It also marks the end of the maximum ejection phase and the beginning

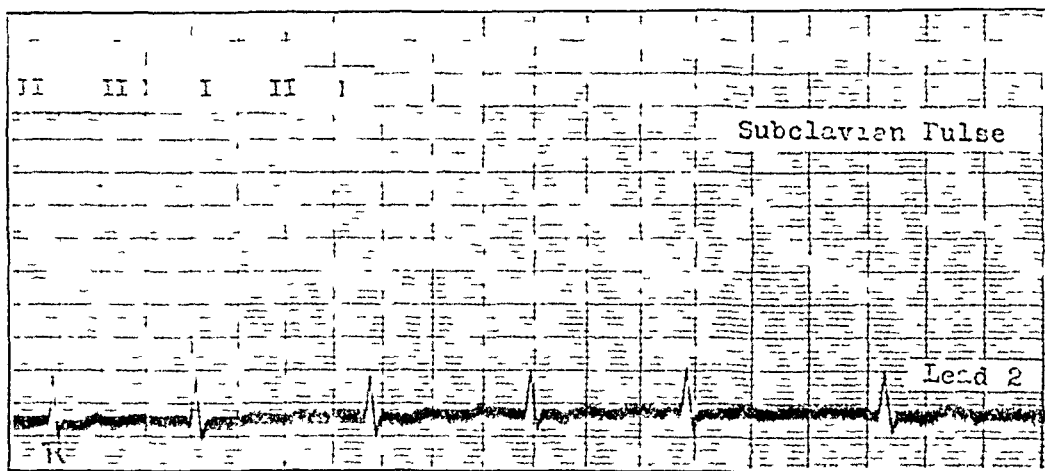


Fig 8—Simultaneous record of heart sounds (top curve), subclavian arterial pulse (middle curve), and electrocardiogram, Lead II (bottom curve) from a case of auricular fibrillation. *M*, diastolic murmur, *I* and *II* first and second heart sounds, respectively.

of reduced ejection (Wiggers<sup>1</sup>). The size of the pulse, therefore, actually indicates only the amount of blood ejected during the maximum ejection phase. It gives no indication of the output during reduced ejection, because the latter occurs at the beginning of the descending limb of the pulse (catacrotus). However, it has been found that in animals the output during maximum ejection not only constitutes the major portion of the total systolic discharge, but it also varies more or less proportionately with the latter under a large variety of conditions (Wiggers and Katz<sup>2</sup>). The changes in pulse size are therefore interpreted as indicating, to a fair degree of accuracy, the variations in relative systolic discharge.

14 Frank, O. *Ztschr f Biol* 46 478, 1905

ceeding total systoles. These shorten only slightly with the shortening of diastole and show many independent variations. Figure 6, *C* represents the duration of the ejection phases. These vary more than the total systole and follow the duration of the preceding diastole more closely but with occasional exceptions. Figure 6, *D* indicates the duration of the isometric contraction phases. This period varies with the duration of the preceding diastole with only few exceptions, but in the opposite direction, it lengthens as the diastole shortens. This effect of the diastole on the isometric period accounts for the relatively more constant duration of total systole, for the latter is from this point of view the sum of its phases, and these vary in opposite directions.

These findings confirm and extend those of Weitz,<sup>13</sup> who obtained similar results in a smaller series of clinical cardiac arrhythmias by a different method, but which is not free from criticism.

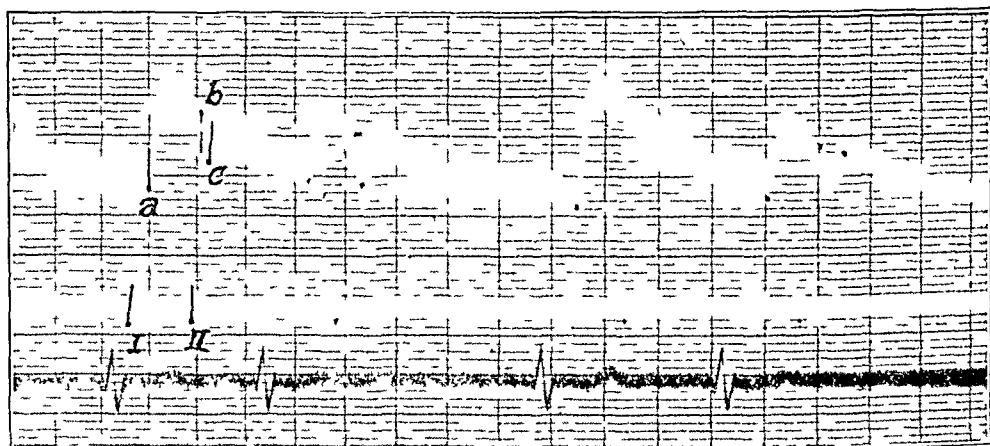


Fig 7—Simultaneous record of heart sounds (middle curve), subclavian arterial pulse (upper curve) and electrocardiogram, Lead II (bottom curve) from a case of auricular fibrillation

*The Effect of Changing Cycle Length on the Size of the Pulse in Successive Beats*—In studying successive beats in the central pulse by optical means (such as Figs 4, 7 and 8), we find that the changes are the same as in the radial pulse. As a rule, large beats succeed long diastolic pauses and small beats follow short intervals. At times, however, small beats succeed long pauses, and vice versa. In general, the size of each beat varies directly with the length of the preceding diastole but not proportionately. There is a greater variability in height in beats with short preceding diastoles. Slight differences in diastole cause greater changes in height in these beats than in those occurring after longer pauses.

contraction is the important factor in determining the duration of the isometric period, or conversely, that the rapidity of ventricular contraction is fairly accurately given, within limits, by the duration of the isometric period. This last agrees with the observation of Wiggers<sup>2</sup> that the duration of the isometric contraction period is determined by the initial tension because, so we infer, it alters the rapidity of ventricular contraction.

*Discussion*—The effects of changing cycle length in cases of auricular fibrillation are in close agreement with recent results obtained on experimental animals, and they follow the same laws. The duration of systole and its phases, the height of the beat and the rapidity of contraction all depend, in the first place, on the initial tension and diastolic volume of the ventricle, and in the second place, on the condition of the myocardium. The predominant influence of the duration of the preceding diastole results from its effect on these two factors, by modifying the duration of filling it determines the initial tension and diastolic volume of the ventricle, and by modifying the period of rest it determines the condition of the myocardium. The changes in arterial resistance (diastolic blood pressure) that result from the variations in the duration of diastole may play some part, particularly in hypodynamic hearts as Einthoven and Korteweg<sup>16</sup> held, but this, we believe, is of relatively minor importance.

The occasional deviation from this influence of diastole can be explained by the action of other influences on the initial tension and condition of the myocardium, as in the experimental and normal cases. These influences include varying tonus of the cardiac nerves and variations in venous return such as result from respiration because of dyspnea. When failure is present, and it is here that the exceptions are more frequent, we may add the motropic effect of varying oxygen and carbon dioxide tensions of the blood and the influence of changing chemistry of the heart fluids. The deviation may be the result of imperfect or delayed relaxation as suggested by Lewis,<sup>17</sup> or it may, according to Hering's hypothesis,<sup>18</sup> result from the varying quantities of myocardial fibrils in contraction.

Whatever the cause may be, the results confirm the fact that the response of the ventricle in auricular fibrillation, as in normal persons and experimental animals, is modified by other factors than the duration of the preceding diastole. Although the duration of the diastole is the most important, it is not the only influence concerned in the dynamics of ventricular systole.

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16 Einthoven, W., and Korteweg, A. J. *Heart* 6 107, 1915-1917.

17 Lewis, T. *The Mechanism and Graphic Registration of the Heart Beat*, London, 1920, p. 385.

18 Hering, H. E. *Munchen med Wchnschr* 55 931, 1908.

This method of estimating the systolic discharge was used only in studying consecutive beats, because only under such circumstances can we maintain a comparative uniformity of the mechanical factors involved in taking the record, that is, the pressure applied over the subclavian artery and the condition of the recording capsule. The modification which the elasticity coefficient of the aorta and subclavian artery produce is so slight that for estimations such as ours it plays an insignificant rôle. This is probably the simplest clinical method available at present for such determinations in cardiac irregularities. It is more accurate than the usual methods utilizing pulse pressure, in that it is obtained optically. The gas methods used by Zuntz, Plesch, Krogh and others<sup>15</sup> cannot be used in cases of auricular fibrillation because of the great variability in cycle length and pulse size.

We, there, interpret these findings as indicating that changes in the systolic discharge occur in auricular fibrillation, partly as a result of the varying cycle length, but also because of other factors.

*The Effect of the Altering Cycle Length on the Velocity of Ejection*—The relative velocity of ejection in consecutive beats can be readily obtained by dividing the height of the pulse beat (in millimeters) by the duration of the maximum ejection phase (in seconds), the result being expressed in millimeters per second. This gives a truer result than when the height is divided by the duration of the entire ejection in that the height of the pulse actually indicates only the discharge during maximum ejection, as already mentioned. The duration of the maximum ejection phase is given by the time interval between the beginning of the rise and the peak of the pulse. In Figure 6, *c*, the ejection phases are subdivided into the two periods by white lines. The maximum ejection is the portion to the white line, the reduced ejection is the part above.

When the velocity of ejection was determined in this way in successive beats, it was found that almost without exception it varied directly with the size of the pulse, and inversely with the duration of the isometric period. This is graphically shown for a typical case in Figure 6 when one compares the graph of ejection *rate* in this case (Fig 6, *F*) with the height of the beat (Fig 6, *E*) and with the duration of the isometric period (Fig 6, *D*). This indicates, in the first place, that in auricular fibrillation in man, as in animals in whom some arrhythmia is present, the amount of the systolic output varies from beat to beat, not only because of the changing duration of ejection but also because of a change in the velocity of ejection. In the second place, it shows, so we believe, that the rapidity of ventricular

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<sup>15</sup> Zuntz, E. *Ztschr f klin Med* **74** 347, 1912. Plesch, J. *Zentralbl f Physiol* **26** 89, 1912. Krogh, A., and Associates. *Skand Arch f Physiol* **27** 100, 126 and 227 1912.

its ejection phase is also found when the plots of all the beats in the two series are compared. It is not related to the age, to the blood pressure, to the etiology of the fibrillation or to the amount or type of therapy received, but apparently only to the degree of cardiac failure. Contrary to our expectations, the length of systole and its ejection phase is not directly but in a general way more or less inversely proportional to the degree of failure.

In attempting to explain this discrepancy, we studied a case of paroxysmal auricular fibrillation during both mechanisms, and found that under otherwise practically constant conditions the duration of systole and ejection was relatively shorter during a period of auricular fibrillation than during the normal mechanism. We attribute this shortening to the absence of synergic auricular contractions in auricular fibrillation. On this assumption the relative shortening is due to the absence of the auricular contribution to ventricular filling. The relation of this shortening to the degree of failure is explained by assuming that the response of the ventricle to this relatively smaller filling is increased in the failing heart more or less proportionately to the degree of failure. Other mechanisms may operate, but at the present time this one seems the most logical.

4 The constantly changing cycle length in cases with auricular fibrillation permitted the study of its effect on the dynamics of systole.

The relative systolic output during the maximum ejection phase is indicated by the height of successive beats in the optically recorded subclavian pulse, and this height divided by the duration of the *maximum ejection* phase gives the relative velocity of ejection.

In any person with auricular fibrillation, we find that the dynamics of successive ventricular systoles are primarily but not entirely determined by the duration of the preceding diastole. In general, a change in the duration of diastole causes a like change in the succeeding systolic discharge (as indicated by the height of the pulse), in the duration of systole, and in the duration and velocity of ejection, but produces an opposite change in the duration of the isometric period. The more constant duration of total systole in a single case results from the opposite effect of diastole on the durations of the systolic phases.

The occasional deviations from the influence of diastole is explained, as in experimental animals, by the effect of alterations in venous return, in tonus of the cardiac nerves, etc. In view of the pathologic condition of the heart muscle and the failing circulation in some cases, other additional factors probably operate. The alterations in the tension of blood gases, changing chemistry of the heart fluids, imperfect or delayed relaxation (as suggested by Lewis) or other deviations in



Our results show, furthermore, how nicely the ventricle adapts itself to changing dynamics, and our study enables us to formulate a conception of this adapting mechanism

#### SUMMARY

1 A study of optically recorded heart sounds and the subclavian pulse was made in a series of fifteen normal persons and in a series of fifteen persons with auricular fibrillation. A method is given for determining the duration of systole and its phases from these records.

2 As a result of the study of the normal series, which includes almost 500 measurements, we find that with a variation in heart rate from 100 to fifty-four beats per minute, the isometric contraction phase varies from 0.024 to 0.089 of a second, the ejection phase from 0.22 to 0.298 of a second and the total systole from 0.262 to 0.374 of a second. The isometric period varies independent of the rate and of the duration of the other phases, whereas ejection and total systole are determined chiefly but not entirely by the duration of the preceding diastole. The duration of total systole is determined largely by the duration of ejection.

The formula  $S = K/\overline{C}$  was tested and found to be of value in indicating the influence of cycle length on the duration of ejection.

The results in the normal series are in accord with the results of Lombard and Cope and more closely with those of Wiggers and Clough. They also agree with the experimental observations of Wiggers and Katz and follow the same laws.

3 As a result of the study of sixteen series of observations on fifteen cases with auricular fibrillation, which includes about 1,500 measurements, we find a greater variation in the cycle length both in the entire series and in individual cases than occurs in the normal series, and with this there is a greater variability in the duration of systole and its phases. With a predominant heart rate ranging from 186 to forty-six beats per minute, the isometric contraction period varies from 0.006 to 0.152 of a second, the systolic ejection phase from 0.055 to 0.293 of a second and the total systole from 0.096 to 0.37 of a second.

On comparing the average durations in the two series we find that in auricular fibrillation, as in the normal cases, the duration of the average systole and its ejection phase is determined chiefly, but not entirely, by the duration of the corresponding average diastole.

The isometric period is on the whole slightly longer than normal, but like the isometric period of the normal person, it bears no relation to the predominant rate or the average duration of the other phases.

Much more striking is the fact that the average total systole, and more particularly the average ejection phase, is shorter than normal at corresponding rates. This relative shortening of total systole and

# LAMBLIA (GIARDIA) INFECTION ASSOCIATED WITH CHOLECYSTITIS

REPORT OF A CASE TREATED WITH NEO-ARSPHENAMIN<sup>1</sup>

JOHN L. KANTOR, M.D.

NEW YORK CITY

## INCIDENCE

It is now generally agreed that *Lamblia* infection of the intestinal tract is not as rare as it was thought to be before the World War Surveys in America and in Europe indicate that lambliasis is possibly the second most common of the protozoal infections, being surpassed in frequency only by endamebiasis (Hegner and Payne,<sup>1</sup> Fantham and Porter,<sup>2</sup> Kofoed, Kornhauser and Plate<sup>3</sup>) In children, at least in those in institutions, the infection is even still more common than in adults (Maxcy<sup>4</sup>)

## DIAGNOSIS

Until recently the diagnosis of *Lamblia* infection could be made only by an examination of the stools With the increased employment of the intestinal (duodenal) tube, the diagnosis can also be established simply by direct microscopy of the aspirated duodenal contents Since the active, flagellate form of the parasite is found in the duodenum, it is not necessary to employ the differential staining methods required to identify the encysted forms in the stools Whether the tube method is more accurate than the stool method in the sense of revealing a greater number of infections, has not yet been established Owing to their lightness and to the concentration of the protozoa in the upper intestine, one might expect the tube method of diagnosis to be clinically effective This is not the case with a nonprotozoal inhabitant of the upper intestine, namely the hookworm, as I found that the aspiration of uncinaria ova for the purpose of diagnosis—even in heavily infected carriers—occurred far too seldom to be of any value as a diagnostic measure In the case of *Lamblia*, therefore, special comparative studies of this nature would be welcome

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\* Read at the Twenty-Sixth Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., May 1, 1923

1 Hegner, R. W., and Payne, G. C. Surveys of the Intestinal Protozoa of Man in Health and Disease, *Sc. Month* **12** 47-52, 1921

2 Fantham, H. B., and Porter, A. The Pathogenicity of Giardia (Lamblia) Intestinalis to Men and to Experimental Animals, *Brit. M. J.* **2** 139-141, 1916

3 Kofoed, C. A., Kornhauser, S. L., and Plate, J. T. Intestinal Parasites in Overseas and Home Service Troops of the U. S. Army, *J. A. M. A.* **72** 1721-1724 (June 14) 1919

4 Maxcy, K. F. Giardia (Lamblia) Intestinalis, a Common Protozoan Parasite of Children, *Bull. Johns Hopkins Hosp.* **32** 166-170, 1921

ventricular filling, and variations in the number of contracting ventricular fibrils (according to Hering's hypothesis) are suggested as possible causes

In addition, this study shows that the variations in systolic discharge are the product of two other variables, namely, the rate of ejection and its duration

It shows further that with certain reservations the duration of the isometric period is an index of the rapidity of ventricular contraction

5 We conclude from these observations that in man, as in animals, the changes in the dynamics of ventricular systole occur primarily as a result of changes in two factors, the one physiologic, that is, the condition of the myocardium, and the other physical, that is, the tension and volume of the ventricle at the beginning of systole

and that is the tendency of the organism to invade the bile passages and the gallbladder. Six years ago, Smithies reported the actual presence of *Lambli*a in an infected gallbladder removed at operation. Since that time several other authors have made incidental mention of associated symptoms strongly pointing to gallbladder involvement (B. B. V. Lyon,<sup>6</sup> Simon,<sup>8</sup> Hollander,<sup>9</sup> Knighton<sup>10</sup>). I shall focus attention further on the question of *Lambli*a cholecystitis.

#### THERAPY

Until recently lambliasis, at least in the severe form, has been regarded by many discriminating workers as being practically incurable. The large number of therapeutic procedures that have been tried and found wanting has often been recorded. Dobell and Low,<sup>14</sup> in a well controlled case, failed completely with bismuth salicylate, beta-naphthol, methylene blue, turpentine, and guaiacol carbonate. Cade and Hollande<sup>15</sup> were similarly disappointed with emetin hydrochlorid given hypodermatically, emetin bismuth iodid by mouth, salicylic acid, hydrochloric acid, quinin sulphate, picric acid, and arsphenamin by mouth. Simon failed to cure by transduodenal lavage with Jutte's hypertonic saline solution, and I failed with similar lavage with strongly acidulated saline. In this connection, as in all parasitic infections, it should be borne in mind that the criteria of cure are to be strictly followed, it having been shown, particularly by Dobell and Low, and by Porter,<sup>16</sup> that a long period of observation is absolutely necessary to insure a safe verdict as to the results of therapy.

It was not until 1917 that any real hope for the successful treatment of giardiasis was forthcoming. In that year, Yakimoff<sup>17</sup> and his co-workers showed definitely that arsphenamin was capable of killing *Lambli*a. These workers experimented with mice and checked their results carefully by postmortem examination. Similar findings were obtained subsequently in this country by Kofoed and his associates, who succeeded in curing *Lambli*a-infested rats by administering massive doses of neo-arsphenamin. In 1918, Cade and Hollande and Goiffon and Roux<sup>18</sup> treated human giardiasis with arsphenamin and neo-arsphenamin but obtained indifferent results. In all probability, as

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14 Dobell, C., and Low, G. C. A Note on the Treatment of *Lambli*a Infections, *Lancet* **2** 1053, 1916.

15 Cade, A., and Hollande, A. C. L'Entérite à "Giardia (*Lambli*a) Intestinalis," *Arch. d. mal. d. l'app. digestif* **10** 193-222, 1919.

16 Porter, A. An Enumerative Study of the Cysts of *Giardia* (*Lambli*a) Intestinalis in Human Feces, *Lancet* **1** 1166-1169, 1916.

17 Yakimoff, W. L., Wassilevski, W. J., and Zwietkoff, N. A. Sur la chimiothérapie de la lambliose, *Sciences et mem. Soc. Biol.* **80** 506-507, 1917.

18 Goiffon, R., and Roux, J. C. Les entérites à *Lambli*a, *Arch. d. mal. d. l'app. digestif* **9** 601-615, 1918.

More and more cases of lamblasis, however, are now being recognized by duodenal aspiration. In most cases this has been an accidental finding in the course of bile drainages for other—diagnostic or therapeutic—purposes. The original publication of M. W. Lyon,<sup>5</sup> who found *Giardia* in the duodenal contents of two patients at the Walter Reed Hospital, was followed by similar reports from B. B. V. Lyon,<sup>6</sup> Smithies,<sup>7</sup> Simon,<sup>8</sup> Hollander,<sup>9</sup> and Knighton<sup>10</sup> in this country, and by Boyd<sup>11</sup> in Canada. In the author's case also the diagnosis was made by this method.

#### PATHOGENICITY

The most common clinical condition associated with *Lamblia* infection is an enterocolitis. It is now recognized that diarrhea need not invariably occur in the presence of infestation with this parasite. In this respect one is reminded of the growth of our knowledge concerning *Strongyloides intestinalis*, which was at first thought to be directly associated with Cochin-China diarrhea. When diarrhea is not present, the enterocolitis of lamblasis may be expressed by other symptoms such as constipation, irregular bowel action, colic, and the presence of mucus in the feces. The facts pointing most strongly to the pathogenic rôle of *Lamblia* has been well presented by Fantham and Porter, who found postmortem, destructive changes in the intestinal epithelial cells, and by Fairise and Jannin<sup>12</sup> as well as by Kofoid and Christansen,<sup>13</sup> who found the parasite embedded in the deeper layers of the intestinal mucosa.

There is, however, another aspect of the pathogenicity of *Lamblia* infection which is, or at least might well be, of great clinical interest,

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5 Lyon, M. W. Intestinal Parasites During a Year at the Walter Reed General Hospital, J. A. M. A. **72** 326-327 (Feb. 1) 1919.

6 Lyon, B. B. V., Bartle, H. J., Ellison, R. T., and Richardson, R. Discussion of the Treatment of a Case of Chronic Arthritis, with Lamblasis, by Duodenal Biliary Drainage, Med. Clin. N. A. **4** 1153-1171, 1921.

7 Smithies, F. The Frequency of Protozoic Enterocolitis in the Middle West. Clinical Manifestations, Diagnosis and Treatment, Am. J. M. Sc. **156** 173-184, 1918.

8 Simon, S. K. *Lamblia* Intestinalis Infestation Successfully Treated by Transduodenal Lavage. Report of a Case, Tr. Sect. Gastro-Enterol. & Proctol., A. M. A. 1921, pp. 151-159. Further Observations of *Lamblia* Intestinalis Infestation and Its Treatment, South. M. J. **15** 458-462, 1922.

9 Hollander, E. Personal Communication.

10 Knighton, J. E. *Lamblia* Intestinalis with Report of Cases, South. M. J. **15** 457-458, 1922.

11 Boyd, W. The Detection of *Lamblia* (*Giardia*) Intestinalis by Means of the Intestinal Tube, Canad. M. A. J. **11** 658-660, 1921.

12 Fairise, C., and Jannin, L. Dysenterie chronique a *Lamblia*, etude parasitologique et anatomo-pathologique, Arch. d. med. exper. et d'anat.-path. **25** 525-551, 1913.

13 Kofoid, C. A., and Christansen, E. B. On *Giardia microti* sp. nov., from the Meadow Mouse, Univ. Calif. Publ. Zool. **16** 23-29, 1915.

strating that soon after its intravenous injection the arsphenamin leaves the blood and becomes deposited or fixed in certain natural depots of the body, such as the liver, kidneys and spleen. At this early date, the excretion of the arsenic was being actively studied in the urine, particularly by Abelin<sup>23</sup> (1911), but its excretion in the stools, though recognized even by the earliest workers, was not accorded sufficient attention. As far back as 1912, Ullmann<sup>24</sup> found from experiments in rabbits that not only do the liver, kidneys and spleen fix the arsenic, but that even a few minutes after its injection the drug arrives in the gastro-intestinal tract—probably in the blood vessels and glands thereof—where it is in part fixed and in part excreted through the intestinal secretions and dejecta, to be in turn partially reabsorbed through the portal circulation.

In 1913, Frenkel-Heiden and Navassart<sup>25</sup> showed by a comparative study of the urine and feces that from two to ten times as much arsphenamin is excreted by the intestine as by the kidneys. That arsenic is excreted by the stomach was shown as early as 1910 by Jeanselme, Bongrand and Chevalier,<sup>26</sup> who found about 0.01 gm arsenic in the vomitus of a patient who had received 0.6 gm arsphenamin five to eight hours previously.

In 1914, Stuehmer<sup>27</sup> confirmed the presence of arsenic in the stomach and small intestine and was apparently the first to attempt to demonstrate its presence in the bile. His results proved inconclusive, but as he likewise failed to find arsenic in the stool, it seems fair to conclude that his methods were perhaps at fault.

Probably the first to show that arsenic was actually excreted through the bile was Pomaret<sup>28</sup> (1920), who injected 0.3 gm neo-arsphenamin into a dog, fixed a cannula in the common bile duct, and recovered within one hour arsenic corresponding to more than 0.01 gm of arsphenamin. Incidentally, the amount thus excreted through the biliary system was found to be greater than that excreted by the kidney in the same interval.

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23 Abelin, J. Beginn u. Dauer der Ausscheidung des Salvarsans nach intravenöser Injektion, *München med Wchnschr* **58** 1771-1773, 1911.

24 Ullmann, K. Ueber Ausscheidungswerte u. Speicherungsverhältnisse nach Einfuhr von Salvarsan in der menschlich-tierischen Organismus, *Arch f Dermat u Syph* **114** 511-570, 1912.

25 Krenkel-Heiden and Navassart. Ueber das Schicksal des Salvarsans im menschlichen Körper, *Ztschr f exper Path* **13** 531-542, 1913.

26 Jeanselme, E., Bongrand, J. C., and Chevalier, P. Sur le rythme de l'élimination de l'arsenic après l'injection intramusculaire ou sous-cutanée de produits organo-arsénicaux solubles et en particulier d'hectine, *Bull et mem. med d hôp de Paris* **30** 743-752, 1910, ser 3.

27 Stuehmer, A. Zur Topographie des Salvarsans und Neosalvarsans, *Arch f Dermat u Syph* **120** 589-610, 1914.

28 Pomaret, M. L'élimination des arsenobenzols, *La med* **2** 123-125, 1920.

is now apparent, their initial dosage was too small. In 1920, however, Carr and Chandler<sup>19</sup> reported the cure of a case by a series of four intravenous injections of neo-arsphenamin 0.6 gm each. Dr. Chandler writes to me that this case has remained negative for two and a half years, as proved by repeated stool examinations. It may therefore be regarded as the first carefully controlled cure of this disease on record.

In a further communication, Dr. Chandler says

The successful employment of neo-arsphenamin in the treatment of intestinal protozoal diseases depends entirely on getting enough of this product, or whatever modification of it reaches the intestine, into the intestine at one time to kill the organisms present. For *Giardia* we have found that in patients 25 to 30 years of age who do not have an intensive intestinal ulceration three injections of 0.6 gm at five day intervals are sufficient to take care of the infection. However, if the secretory function of the gut is impaired through age or extensive ulceration, a larger dose, at least a larger initial dose—usually 0.9 gm—is required to accomplish the desired results. If in the treatment of intestinal protozoal diseases the initial dose is small (0.3 gm or less) the invading organism appears to develop a tolerance to neo-arsphenamin to such an extent that later larger doses often fail to destroy it.

The last sentence is of particular significance and might serve to explain many of the failures described in the literature. Since the publication of Carr and Chandler's case, two communications reporting treatment with neo-arsphenamin have appeared, one by Reverdin and Chomé,<sup>20</sup> the other by Simon.<sup>8</sup> The Swiss authors mention one case which they treated with five injections (dose not stated) at three day intervals and which remained negative for the nine months to date of publication. Simon administered the drug to five patients, four times intravenously, and once through the duodenal tube. Unfortunately, the dose—with one exception—was not stated, and the observation of results after treatment was apparently not exhaustive. The immediate effects, however, were quite satisfactory.

The question now naturally arises, In what way is arsphenamin or its congeners effective in ridding the organism of intestinal protozoa? A survey of the literature bearing on arsphenamin and its behavior in and excretion from the body has proved most fascinating. Soon after the introduction of arsphenamin by Ehrlich in 1910, studies began to appear on the fate of the drug in the body. Such workers as Fischer and Hoppe<sup>21</sup> (1910) and Bornstein<sup>22</sup> (1911) succeeded in demon-

19 Carr, E. I., and Chandler, W. L. Successful Treatment of Giardiasis in Man with Neo-Arsphenamin, *J. A. M. A.* **74** 1444-1445, (May 22) 1920.

20 Reverdin, A., and Chomé, E. *Lamblia intestinalis*, *Rev. med. de la Suisse Romande* **42** 118-119, 1922.

21 Fischer, P., and Hoppe, J. Das Verhalten d. Ehrlich-Hataschen Präparate im Menschlichen Körper, *München med. Wchnschr.* **57** 1531-1532, 1920.

22 Bornstein, A. Ueber das Schicksal des Salvarsans im Körper, *Deutsch. med. Wchnschr.* **37** 112-113, 1911.

## SUMMARY AND CONCLUSION

1 Arsenic disappears from the blood soon after intravenous injection

2 It is fixed in certain natural depots of the body, particularly in the digestive canal and the liver, and to a less extent, in the kidneys and spleen

3 Arsenic excreted into the intestinal tract is in part eliminated through the feces, but is in part also reabsorbed through the portal circulation

4 The liver excretes arsenic into the bile in relatively large quantities

5 Arsphenamin administered by rectum in large enough doses probably behaves systemically in the same way as when given intravenously

It follows from the foregoing that we have in arsphenamin or neo-arsphenamin therapy a precise and effective method of reaching susceptible protozoan parasites no matter how deeply they may invade the intestinal or biliary mucosa

## REPORT OF A CASE

*History* (April 20, 1922)—Miss L. M., aged 30, a trained nurse, referred by Dr. Ira Cohen, was born in Michigan, where she lived until she came to New York City in 1907. About twelve years ago she began to have pains in the right side of the abdomen, radiating to the groin, interfering when she walked, and becoming more marked before the menstrual periods. There was never actual prostration, nor was there any vomiting, abdominal rigidity or fever. The bowels moved habitually two or three times a day. More frequent and looser movements might have occurred at times, but the patient was not certain about this.

Seven years after the onset of these pains the patient was operated on, and a "clean" appendix was removed. While in bed following the operation, she experienced pains at the waist line with radiation to the back. Roentgenograms of the kidney region proved negative for calculi. The patient remained free from symptoms for a period of two years following the operation.

Three years ago the pains recurred, but they were located higher up than originally, extending under both rib margins and radiating to the back between the shoulder blades. The attacks generally took place at 9 or 10 p. m. As before, they showed a tendency to come on with the menses, except that for the past three months they had become practically constant.

During the past year there was increasing abdominal distention, especially after meals, and more marked on the right side. Recently the upper part of the abdomen had become so sensitive that the pressure of the corset or of any tight waist bands caused extreme discomfort. At no time had there been jaundice.

*Examination*—This revealed a stocky young woman, 20 pounds (9.07 kg.) overweight, not acutely ill, who was organically sound except for a liver that was palpable about two fingerbreadths below the right costal margin and which was distinctly tender on pressure. There was no jaundice and no fever. The urine was negative, except for an excess of indican.



During the past year (1922), three important chemical studies have appeared in this country by Voegtlin and Thompson,<sup>29</sup> by Underhill and Davis,<sup>30</sup> and by Clausen and Jean,<sup>31</sup> all definitely showing that arsenic is excreted far more profusely by the gastro-intestinal tract than by the urinary system. These findings show that the same is true of arsenic that has already been experimentally demonstrated for mercury and other heavy metals, namely, that "the chief channel of elimination is by way of the bowel and relatively little of these substances can be made to pass out by way of the urine under any circumstances (Sansum<sup>32</sup>)". The actual rate of excretion of arsenic into the intestinal tract varies with the different arsenicals, Voegtlin and Thompson having shown that it amounts, within the first twenty-four hours, to the surprising proportions of 33 per cent of the dose injected in the case of neo-arsphenamin and 82 per cent of the dose in the case of arsphenamin. The same authors have also found that the "bile contains considerable amounts of arsenic after the intravenous injection of arsphenamin and neo-arsphenamin" (Personal communication).

At this point a few remarks as to the administration of arsphenamin by rectum may be in order. In several of the cases of lamblasis reported since the era of arsphenamin protozootherapy it was remarked that the intravenous mode of administration was refused by the patient. In the case I report the veins were so small as to cause unusual difficulty in consummating this form of treatment. In all such cases, as well as in children, it is quite possible that the drug may be exhibited successfully per rectum. Boyd and Joseph<sup>33</sup> (1918) were the first in this country to advocate this type of therapy. It has more recently been shown by Mehrtens<sup>34</sup> (1921) that when arsphenamin is administered by rectum in sufficiently large doses, arsenic is absorbed into the blood, that it persists there longer, and that larger quantities are eliminated in the urine (and presumably reexcreted into the intestine) than after the ordinary intravenous administration. To achieve this purpose, Mehrtens recommends a dosage of 4 gm of neo-arsphenamin.

29 Voegtlin, C, and Thompson, J W. Rate of Excretion of Arsenicals a Factor Governing Toxicity and Parasiticidal Action, *J Pharmacol & Exper Therap* **22** 85-105, 1922

30 Underhill, F P, and Davis, S H. The Excretion of Arsenic After Serial Administration of Arsphenamin and Neo-Arsphenamin, *Arch Dermat & Syph* **5** 40-50 (Jan) 1922

31 Clausen, S W, and Jean, P C. Distribution and Excretion of Arsenic After Intravenous Administration of Arsphenamin in Children, *Am J Syphilis* **6** 556-567, 1922

32 Sansum, W D. The Principles of Treatment in Mercuric Chlorid Poisoning. An Experimental Study, *J A M A* **70** 824-828 (March 23) 1918

33 Boyd, A S, and Joseph, M. Intrarectal Administration of Arsphenamin, *J A M A* **71** 521-523 (Aug 17) 1918

34 Mehrtens, H G. Rectal Injection of Massive Doses of Neo-Arsphenamin, *J A M A* **76** 574-576 (Feb 26) 1921

difficult on account of the obesity of the patient and the smallness and inaccessibility of her veins, were successfully administered by Dr Fred Wise, who reported his findings as follows

"Miss L. M. received, on Oct 7, 1922, a preliminary 'desensitizing' injection of 0.2 gm neo-arsphenamin. There being no reaction within one hour, she received the balance of 0.7 gm. Except for a recurrence of her diarrhea during the following night, there were no untoward effects from the injection of 0.9 gm neo-arsphenamin.

On October 12 the patient received 0.9 gm neo-arsphenamin. Two days later there was a severe reaction manifested by conjunctival injection, headache, fever (102 F), vomiting, pains in the chest and abdomen and diarrhea. The patient noticed that the stools had an unusual odor. The skin exhibited a universal erythematous eruption, in part also urticarial, associated with itching. After five days all symptoms subsided. There was no desquamation.

On October 28, the patient received the third and last injection of 0.9 gm neo-arsphenamin. There was a moderate reaction two days later in every way similar to that of Oct 14, but very much milder. This subsided after three or four days and left the patient in an apparently normal condition.

The urine, examined between the days of the injections, was free from albumin and casts and sugar. At no time was there jaundice."

Duodenal drainage, performed on Oct 22—ten days after the second injection of neo-arsphenamin—showed for the first time complete absence of *Lambli*a from the recovered fluid. On October 28, within an hour of the last injection, the duodenal tube was again introduced and the bile drained for from three to four hours. During this interval three stools were passed and collected. The bile (which was for the second time negative for *Lambli*a) and the stools were submitted to Dr Joseph Felsen, who reported all specimens negative for arsenic by the Gutzeit method. The stools also failed to show either the free or the encysted forms of the parasite.

*Subsequent Course*—In addition to the two negative bile drainages already mentioned (Oct 22 and Oct 28), ten more drainages were made during the six months since the treatment was given (see table). On every occasion the duodenal contents were free from every trace of *Lambli*a infection. In addition to the stool examination of Oct 28, six subsequent tests (also shown in the table) likewise proved negative for this parasite.

As a contrast to the immediate cure of *Lambli*a infestation as such, the clinical condition of the patient has shown only partial amelioration. The liver can no longer be felt and the abdominal tenderness is much less marked and at times quite absent. There have been periods of diarrhea, however, lasting as long as ten days, with as many as ten stools during the twenty-four hours. At times there has been constipation. The bowels have moved loosely three or four times a day on the average, at least for the past few months. Occasionally there has been pain, both in the right side and in the back, worse on motion and interfering especially with walking and with stair climbing. In short, there is still some colitis and perhaps some cholecystitis, and it is probably too early to say just how much these factors have been affected by treatment.

#### NATURE OF THE CHOLECYSTITIS

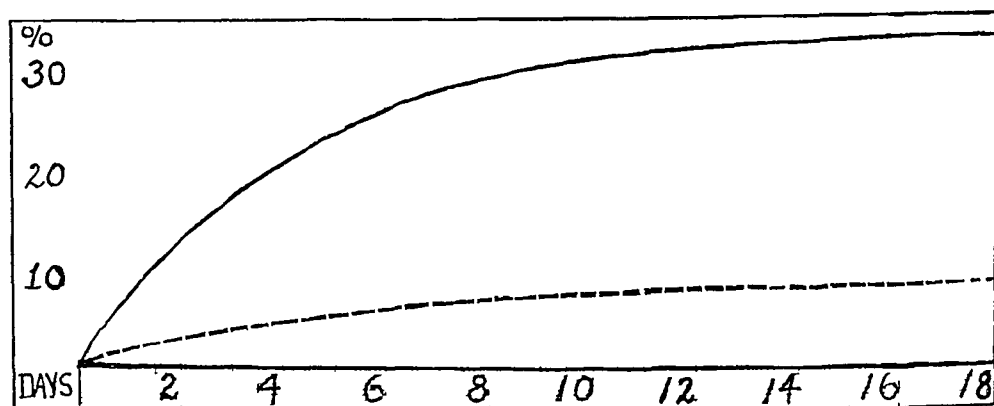
That there was clinically an inflammation of the gallbladder is beyond question. It has already been pointed out that *Lambli*a does actually invade the gallbladder and that many, if not the majority, of the cases now being discovered by duodenal aspiration occur in patients suffering clinically from gallbladder trouble. Despite this fact, the most recent general works on diseases of the biliary passages fail to

Intubation of the stomach showed that it was empty when fasting. After an Ewald test breakfast free acid was absent, the total acidity was 17. Roentgen-ray examination of the digestive tract was negative as regards form and function, except that there was a persistent shallow filling defect on the outer (right) aspect of the duodenal cap.

**Diagnosis**—In view of the history, the tenderness and enlargement of the liver, the achlorhydria and the defect in the duodenal cap corresponding to the region of the gallbladder, a diagnosis of subacute cholecystitis was made.

**Treatment**—As there seemed no urgent indication for surgical intervention, routine medical treatment was instituted. On May 3, 1922, a duodenal tube was introduced for the purpose of effecting bile drainage. The sediment of the recovered fluid was found, on microscopic examination, to contain innumerable, actively motile flagellate organisms readily identified as *Lamblia intestinalis* (*Giardia enterica*).

In view of Simon's then recent report of an apparent cure of *Lamblia* infestation by a series of transduodenal flushes with Jutte's solution, a similar plan of therapy was decided on. From May 3 to May 11, inclusive, the patient received four flushes of 900 c.c. each of hypertonic saline (sodium sulphate and



Arsenic excretion (after arsphenamin injection) in urine and feces as percentage of the injected dose, showing the relatively greater excretion in the feces, the slow excretion after from eight to ten days, and that after two weeks about 50 per cent of the arsenic is not yet excreted (after Clausen and Jean). The continuous line indicates the arsenic excretion in the feces, the broken line that in the urine.

sodium chlorid, 9 parts each per 1,000). As there was no apparent diminution in the number of flagellates present in the duodenal contents, it was decided to add hydrochloric acid to the flush solution in the hope of rendering the environment unfavorable to the parasites, it being commonly supposed that gastric anacidity is a predisposing factor to protozoal infestation. Accordingly, decinormal hydrochloric acid was added to the flush solution in amounts varying from 30 to 210 c.c., increasing the free acidity of the whole wash to a maximum of 22 degrees to the Topfer reagent. Six of these acid flushes were given in all, the last (tenth) flush of the series taking place on May 24, 1922.

The result of this acid flush treatment was disappointing. From the end of May to the end of June the patient suffered from persistent pain and had, in addition, an attack of diarrhea with as many as ten watery stools a day. In July, the symptoms subsided, but an eleventh bile drainage, carried out as a check at the end of September, still showed *Lamblia* present in the duodenum.

At this point it was decided to use neo-arsphenamin intravenously, according to the method of Carr and Chandler. Three injections, which were technically

mentioned that the peculiar odor of the stools was not noticed by the patient until an interval of about two days after the injections

#### COMMENT

What has been notably lacking in the cases published hitherto is the proof, by systematic reexaminations over sufficiently long periods after treatment, that patients are completely and permanently rid of the parasitic invaders. It has been my object, in the case reported, to make this demonstration as thorough as possible during the time interval available for this purpose. There is no question in my mind that the duodenum and the biliary system of my patient are free from *Lamblia*. It is perhaps possible that cysts from some focus lower down in the intestine have been overlooked in the stools. I hope to keep the patient under observation and to report results at some future time.\*

#### CONCLUSIONS

1 *Lamblia* infection is sufficiently common to invite the diagnostic and therapeutic interest of all physicians

2 The positive diagnosis of lambliasis may be made from an examination of the stools for cysts, or even more readily, of the duodenal contents for the flagellate forms

3 *Lamblia* infection is manifested clinically by a colitis, with or without diarrhea, and probably commonly by an associated cholecystitis as well

4 *Lamblia* infection cannot be uprooted by treatment with drugs acting only from within the intestinal lumen. We have in the intravenous administration of arsenicals (arsphenamin) a powerful and perhaps a specific method of attack. The success of this treatment is due to the secretion of arsenic by the entire gastro-intestinal and biliary mucosa, thus destroying not only the superficial but also the deep-seated (penetrating) protozoal parasites as well

5 The initial dose of arsphenamin (or neo-arsphenamin) should be as large as possible (equivalent of 0.6 to 0.9 gm. neo-arsphenamin for an adult) so that *Lamblia* organisms do not develop an immunity as they might from smaller beginning doses

6 In order to prevent or at least to detect a tendency to serious immediate reaction to the large dosage recommended, a preliminary small "desensitizing" dose (about 0.2 gm.) should be given. If no untoward effects occur within an hour, the rest of the initial dose may be safely administered

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\* Since the foregoing was written, three more bile drainages (June, July and September, 1923) have similarly proved negative for *Lamblia*

mention this parasite as a possible factor in the production of biliary symptoms. Is it not time to add the concept of *Lamblia* cholecystitis to the other recognized forms of gallbladder infection?

Furthermore, in one of Simon's recent cases (Case 4) strikingly similar in its course to that in the case reported—the clinical observation was carried a step further in that the gallbladder was removed after arsphenamin injections had caused the disappearance of organisms from the bile, and that fresh scrapings from the gallbladder mucosa failed to reveal the presence of *Lamblia* organisms. It seems fair, therefore, to conclude that we have now strong evidence showing that a gallbladder infested with *Lamblia* can be actually freed from its protozoal invaders by the intravenous administration of arsphenamin. If this is really so, we are dealing with what is perhaps the first successful instance of a specific therapy for a known source of gallbladder infection.

Finally, it appears from the observation of our own case as well as that of others, that the elimination of the primary *Lamblia* infection is by no means synonymous with the cure, or at least with the immediate cure, of the associated cholecystitis. This may be because we still get the cases after the original parasitic insult to the biliary mucosa has developed into the ordinary chronic, nonspecific form of cholecystitis. It is to be hoped that the early recognition and treatment of giardiasis—that is, before the biliary symptoms occur—will lead to the complete elimination of this form of gallbladder complication.

#### NATURE OF THE REACTION FOLLOWING NEO-ARSPHENAMIN

Because of its delayed onset it may be assumed that the reaction experienced by the patient was not anaphylactic in the ordinary sense of the term. Perhaps the two most plausible explanations are the following. 1 The systemic upset may have been a response to the sudden destruction of enormous numbers of foreign organisms throughout the digestive tract with the liberation and absorption of hypothetical toxins. 2 The reaction may have been due to the neo-arsphenamin injection itself, owing to the failure on the part of a previously damaged liver to detoxicate the relatively large doses of arsenic which were required by the treatment. This would be in keeping with the accumulating evidence that many of the arsphenamin reactions are due to hepatic insufficiency.

Our failure to find arsenic in the intestinal contents (duodenal and fecal) after the injection of neo-arsphenamin is best explained—assuming that the tests were technically reliable—by the assumption that, owing to the presumably damaged state of the biliary and intestinal mucosa, the excretion of the heavy metal was delayed beyond the few hours during which our specimens were collected. It may also be

# A STUDY OF THE BASAL AND NITROGENOUS METABOLISM IN A CASE OF ACUTE LEUKEMIA DURING ROENTGEN-RAY TREATMENT<sup>\*</sup>

W G LENNOX, M D, AND J H MEANS, M D

BOSTON

The cases of acute leukemia in which the nitrogen balance has been studied have shown a marked nitrogen loss Ebstein,<sup>1</sup> in 1889, reported a case which showed a twenty-four hour urea excretion of 62.7 gm Magnus Levy,<sup>2</sup> in 1898, reported three cases The first had a negative nitrogen balance of 24.8 gm in forty hours, the second a negative balance of 85.4 gm in seven days, the third, in which nitrogen intake was not calculated, a urinary nitrogen which averaged 21 gm a day for seven days Edsall,<sup>3</sup> in 1905, found in his case a negative nitrogen balance of 22.2 gm in twenty-four hours

We have not seen observations on the basal metabolism in acute leukemia, nor have we seen observations on the effect of radiation on the basal or nitrogenous metabolism of patients suffering from this disease Patients with chronic leukemia almost invariably show an increased basal metabolic rate<sup>4</sup> Following successful roentgen-ray or radium treatment the rate falls Such a fall is usually coincident with reduction in the number of immature leukocytes<sup>5</sup> Following radiation, there is increased excretion of nitrogen in the urine<sup>6</sup>

## REPORT OF A CASE

A girl, aged 18 years, entered the East Medical service of the Massachusetts General hospital on Jan 21, 1921 Her family and past history were unimportant She had felt well until three weeks before entrance At that time, while

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<sup>\*</sup>From the medical service and medical laboratory of the Massachusetts General Hospital, aided in part by a gift from Dr William Norton Bullard

1 Ebstein Acute Leukämie und Pseudoleukämie, *Deutsch Arch f klin Med* **44** 343, 1889

2 Levy, Magnus Ueber den Stoffwechsel bei Acuter und Chronischer Leukämie, *Virchows Arch f path Anat* **152** 107, 1898

3 Edsall, D L A Case of Acute Leukaemia with Some Striking Clinical Features, *Tr Assn Am Phys* **20** 279, 1905

4 Murphy, J B, Means, J H, and Aub, J C The Effect of Roentgen Ray and Radium Therapy on a Patient with Lymphatic Leukaemia, *Arch Int Med* **19** 890 (May) 1917 Gunderson, H H The Basal Metabolism in Myelogenous Leukaemia and Its Relation to the Blood Findings, *Boston M & S J* **185** 785, 1921 Boothby, W M, and Sandiford, I Summary of the Basal Metabolic Data on 8614 Subjects with Especial Reference to the Normal Standards for the Estimation of the Basal Metabolic Rate, *Jour Biol Chem* **54** 783, 1922

5 Gunderson, H H Footnote 4

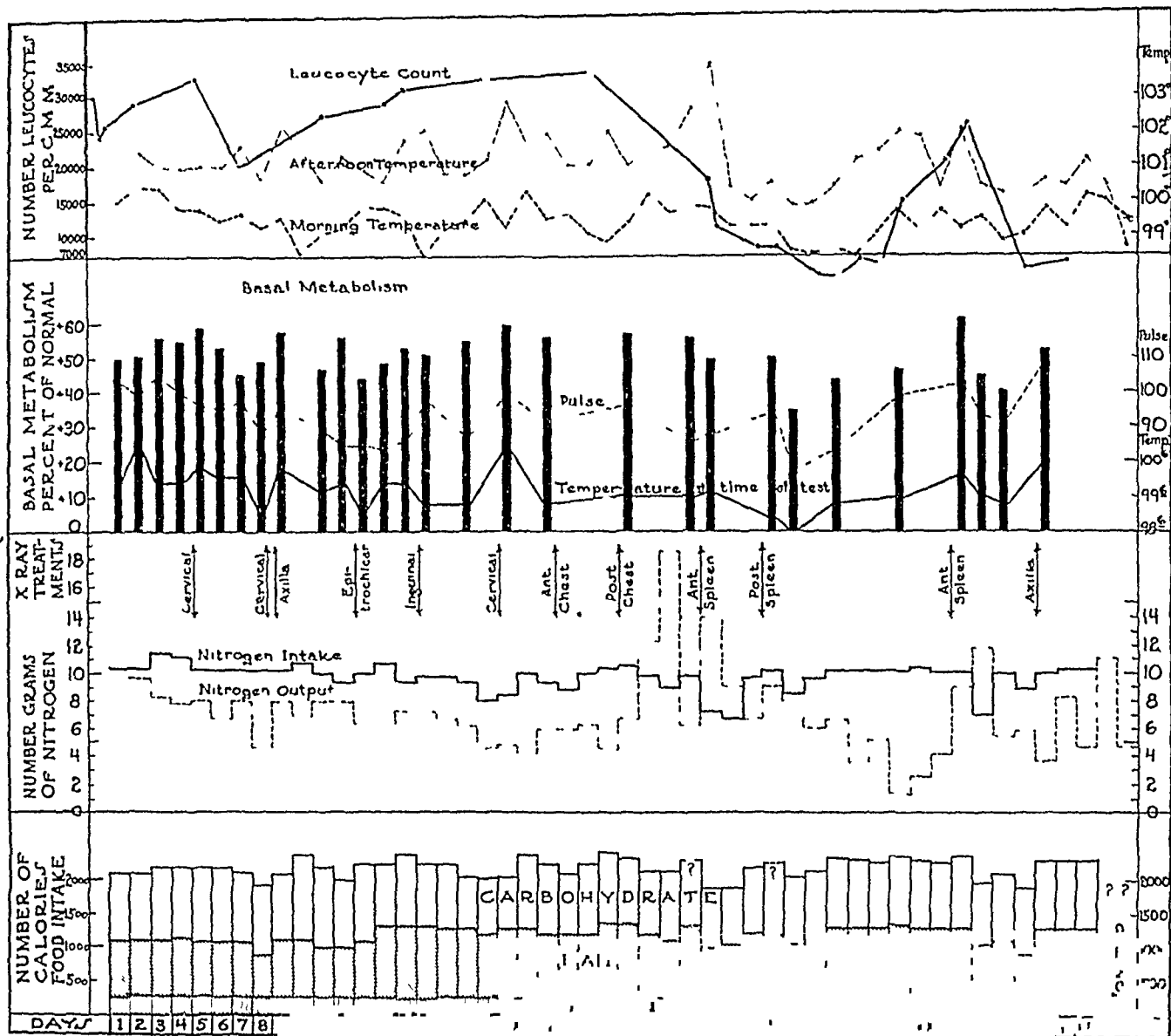
6 Musser, J H, and Edsall, D L A Study of Metabolism in Leukaemia Under the Influence of the X-Ray, *Tr Assn Am Phys* **20** 294, 1905 Ordway T, Tait, J, and Knudson, A Metabolism in Leukaemia and Cancer During Radium Treatment, *Albany Med Ann* **41** 1, 1920

7 When, for any reason, intravenous arsphenamin therapy is not available, it is suggested that satisfactory results may be obtained by the intrarectal exhibition of this drug provided sufficiently large doses (4 gm neo-arsphenamin) are made use of

8 A case is reported of *Lambha* infection associated with cholecystitis and colitis. The parasitic infection promptly responded to three injections of 0.9 gm each of neo-arsphenamin and has remained cured, as shown by repeated reexaminations, for a period of half a year

*Synoptic Review of Therapy in a Case of Lambhasis*

Serial Number of Bile Drainage	Date	Form of Therapy	Lambha	
			In Duodenal Contents	In Stool
	(1922)			
1	May 3	Hypertonic saline flush	+	
2	May 5	Hypertonic saline flush	+	
3	May 8	Hypertonic saline flush	+	
4	May 11	Hypertonic saline flush	+	
5	May 12	Hypertonic plus n/10 hydrochloric acid 30 c c	+	
6	May 13	Hypertonic plus n/10 hydrochloric acid 90 c c	+	
7	May 15	Hypertonic plus n/10 hydrochloric acid 90 c c	+	
8	May 19	Hypertonic plus n/10 hydrochloric acid 180 c c	+	
9	May 21	Hypertonic plus n/10 hydrochloric acid 210 c c	+	
10	May 23	Hypertonic plus n/10 hydrochloric acid 110 c c	+	
11	Sept 24	None	+	
	Oct 7	First dose of neo-arsphenamin 0.9g		
	Oct 12	Second dose of arsphenamin 0.9		
12	Oct 22	None	0	
13	Oct 28	Third dose of neo arsphenamin 0.9	0	0
14	Nov 12	None	0	
15	Dec 3	None	0	
	(1923)			
16	Jan 14	None	0	
17	Feb 18	None	0	
18	Mar 10	None	0	0
19	Mar 25	None	0	0
20	Apr 1	None	0	0
21	Apr 8	None	0	0
22	Apr 14	None	0	0
23	Apr 22	None	0	0



The days of observation are indicated at the bottom of the chart. Above this is the daily intake of fat, protein and carbohydrate, expressed in calories. Question marks indicate that an undetermined amount of food was lost because of vomiting. This amount was small except on the last two days, when no food was retained. Above this a solid line marks the grams of nitrogen contained in the food and a dotted line the grams of nitrogen excreted in urine and feces. The double headed arrows indicate the days on which roentgen-ray treatments were given. The words "cervical, axillary," etc., denote the glands which were irradiated. Basal metabolism is represented by solid columns which express the percentage increase above the metabolism of a normal person of the same age and sex and of equal surface area. The solid line connecting these columns indicates the temperature, and the broken line the pulse, at the time of the test, about 11 a. m. At the top of the chart, the lower broken line indicates the early morning temperature and the upper broken line the evening temperature. The solid line represents the leukocyte count.



at her work in a shoe factory, she felt faint and feverish. She walked home and went to bed. Eight days before entrance she became jaundiced, with accompanying headache, nausea and vomiting. At this time, also, her mother noticed swelling of the cervical glands, and a few days later of the inguinal glands. Enlargement of the spleen had not been noted. Her weight was 20 pounds (9 kg.) less than it had been three months before.

On entrance to the hospital, the patient was pale. The cervical, axillary, epitrochlear and inguinal glands were greatly enlarged. The spleen reached to the umbilicus. Fundus examination of the right eye showed two patches of hemorrhage. The urine was negative, the red cells numbered 2,240,000, hemoglobin (Talquist) was 55 per cent, the bleeding time was thirteen minutes, and the clotting time (method of Lee and White<sup>7</sup>) the same. The leukocytes numbered 28,000, a differential count revealed 10 per cent polymorphonuclears, 60 per cent lymphocytes and 28 per cent large mononuclears. Of the red cells, 10 per cent were reticulated and 17 per cent nucleated. On examination of the stained smear, Dr. George R. Minot found erythroblasts of all types present. There was almost no shape variation and slight variation in size but all degrees of polychromatophilia were present. Young red cells were considerably increased. Eosinophils were rare, young polymorphonuclears numbered about 8 per cent and the majority of the cells looked lymphoblastic.

There was some doubt concerning the acuteness of the disease, and it was decided to give the patient the benefit of this doubt and institute roentgen-ray treatment. After the first few weeks, however, the course of the disease was progressively downward. The red cells fell to one million, hemoglobin to 30 per cent and the platelets to 70,000. The white cells were too immature to permit differentiation between the myelogenous and lymphatic forms of leukemia. Blood nonprotein nitrogen remained normal, but blood uric acid rose from 4.7 mg. per 100 cc. of blood on the eighteenth day of the period of study to 8 mg. on the forty-first day. During the last two days of life there were extensive hemorrhages in the skin, intestines and urinary tract. Death occurred eleven weeks after the onset of symptoms. The short duration of the disease and the blood picture justified the diagnosis of acute leukemia. Unfortunately, permission for necropsy was not secured.

#### BASAL AND NITROGENOUS METABOLISM OF PATIENT

Soon after the admission of the patient, we decided to study her basal and nitrogenous metabolism. This was done for a period of fifty days, until death occurred. During this period the patient was on a weighed diet prepared by Miss Campbell, the hospital dietitian. The diet consisted of 65 gm. of protein (supplying 1.4 gm. of nitrogen per kilogram of body weight), 92 gm. of fat (on the thirteenth day increased to 116 gm.), and 240 gm. of carbohydrate. This yielded about 2,050 calories, which was about 10 per cent above the patient's basal requirement. Body weight throughout the period remained nearly constant.

The total nitrogen of the twenty-four hour urine was determined by the colorimetric method.<sup>8</sup> Stools were collected for a period of five days and the contained nitrogen was found to be 1.1 gm. per day.

7 Lee, R. I., and White, P. D. A Clinical Study of the Coagulation Time of the Blood, *Am. J. M. Sc.* **145**: 495, 1913.

8 Folin, O. Laboratory Manual of Biological Chemistry, New York, D. Appleton & Co., 1922, p. 131.

# MELANURIA WITHOUT MELANOSARCOMA<sup>\*</sup>

## REPORT OF A CASE

JOHN P. PETERS, M.D.

NEW HAVEN, CONN.

This case is reported because of the occurrence of melanuria without any evidences during life or at postmortem examination of any abnormal source of production of the pigment.

### CASE REPORT

*History*—W. S., a school boy, aged 13, born of American parents, was admitted to the New Haven Hospital on March 6, 1922, complaining of progressive enlargement of his abdomen and increasing weakness and drowsiness. His family history was not significant. His past history was unimportant except for frequent nose bleed since childhood and headaches occurring with increasing frequency for a year before admission to the hospital. Three months before admission the patient noticed that his abdomen was growing larger. At the same time he began to complain of a constant tired feeling. His mother noticed that he seemed drowsy all the time, and his teacher complained that he fell asleep at school. He also became irritable. Although his weight increased constantly, his appetite diminished. As the enlargement of his abdomen continued, he developed increasing shortness of breath on exertion. His skin also became sallow and yellowish. A week before admission he began to vomit. The vomiting occurred every other day, usually after a meal, the vomitus consisting of thick, yellowish material. With the onset of the vomiting he began to have a slight, dry cough.

*Physical Examination*—Examination on admission revealed a well developed, moderately well nourished boy, lying quietly in bed, apparently in no distress, mentally clear, but rather drowsy and apathetic. His respirations were somewhat rapid and shallow. His skin and mucous membranes were pale, with a slight yellowish tinge, but there was no definite icterus. His hair was black, his natural color apparently somewhat dark, with small freckles on his nose but no evidences of any abnormal pigmented lesion. There were small, herpetic lesions on both lips. His tonsils were moderately enlarged but showed no signs of active inflammation. His lungs showed dulness behind extending as high as the scapular angle on the left and somewhat higher on the right side. Over these areas breath and voice sounds were diminished. The cardiac impulse was diffuse and forcible, extending 14.5 cm. to the left, well beyond the nipple line. Auscultation revealed a systolic murmur, maximum over the pulmonic area, but transmitted also to the apex. The pulse was regular—rate 82—and of good quality. The blood pressure was systolic, 110, diastolic, 60. His abdomen was protuberant, rounded, smooth and tense, with distinct dulness in the flanks and a fluid wave. In the left hypochondrium was a large mass, extending about 7 cm. below the costal margin in the direction of the umbilicus, presenting a sharp edge and descending slightly on deep inspiration. In the midline a sharp edge could be felt about 4 cm. below the xiphoid, but no liver edge could be felt in the right hypochondrium. There was moderate, pitting edema of the feet, legs, thighs and lower part of the trunk. There was no general lymphatic enlargement. The reflexes were normal.

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<sup>\*</sup> From the department of internal medicine of Yale University and the medical service of the New Haven Hospital.

This average amount was added to the urinary nitrogen to give the nitrogen output. Unmeasured but small amounts were lost through occasional nose bleed. During the last two days nitrogen loss through hemorrhage was large. The patient did not menstruate during the period of study. Oxygen consumption was measured by means of a Benedict portable apparatus. Determinations were made with the patient in her own bed in the ward. In order to interfere as little as possible with the patient's meals, determinations were made four hours after her breakfast, a meal largely carbohydrate containing about 500 calories. Oxygen consumption was thus measured under standard, rather than under basal, conditions. Separate experiments on normal subjects showed that in four hours after a meal of this type the metabolism had returned to within 5 per cent of its basal level. Roentgen-ray treatments were given under the direction of Dr. George W. Holmes. In each exposure a suberythema dose was used.

#### SUMMARY

The principal data of this study are presented graphically in the chart. Inspection of the chart reveals these facts:

- 1 The patient maintained a positive nitrogen balance of a gram or two on a normal nitrogen intake of about 10 gm. a day. This finding is contrary to the observations quoted in the beginning paragraph. Our patient showed an unusually low leukocyte count. Apparently the processes of cellular metabolism, such as the relative intensity of leukocyte production and destruction, were different in our patient and those previously reported. This question of the level of nitrogenous metabolism in acute leukemia deserves more extended study.

- 2 The nitrogen balance was little affected by roentgen-ray exposure of the superficial lymph nodes. Radiation of the thoracic glands and the spleen, on the other hand, produced a marked increase in urinary nitrogen. This effect was, however, transitory.

- 3 Leukocyte count and nitrogen balance were, in a general way, reciprocal factors. A rising leukocyte count accompanied nitrogen retention, and a falling count nitrogen loss.

- 4 Leukocyte count, temperature and basal metabolism moved together. The leukocyte count was, however, more labile than the other two. On two occasions the count fell to normal. At these times the evening temperature remained elevated and the metabolism was but little affected. The metabolism seemed to be a truer indicator of the severity of the process than the leukocyte count.

dominantly lymphocytes. No tubercle bacilli could be found on direct smear, and guinea-pigs that had received injections failed to develop signs of tuberculosis.

*Course*—Throughout his stay in the hospital the physical signs remained about the same. There was a constant accumulation of fluid in the abdomen and chest that demanded repeated paracentesis. After the first few days in the hospital he began to show an irregular temperature, rising at times as high as 102 F. Blood cultures were negative, and there was no leukocytosis. Shortly after admission he developed a mild diarrhea, which lasted three or four days. At about the same time the subcutaneous edema increased rapidly, urine volume diminished, and the salt output was found to be very low. The urine showed no morphologic changes, however.

On March 27, three weeks after admission, he was suddenly seized with severe pain in the left flank, not radiating, accompanied by vomiting of undigested food. The vomiting did not relieve the pain. Some diffuse tenderness was found in the left flank, and red blood cells appeared in the urine. The tenderness and hematuria lasted only a few days. About this time, distention of the abdominal veins became quite striking.

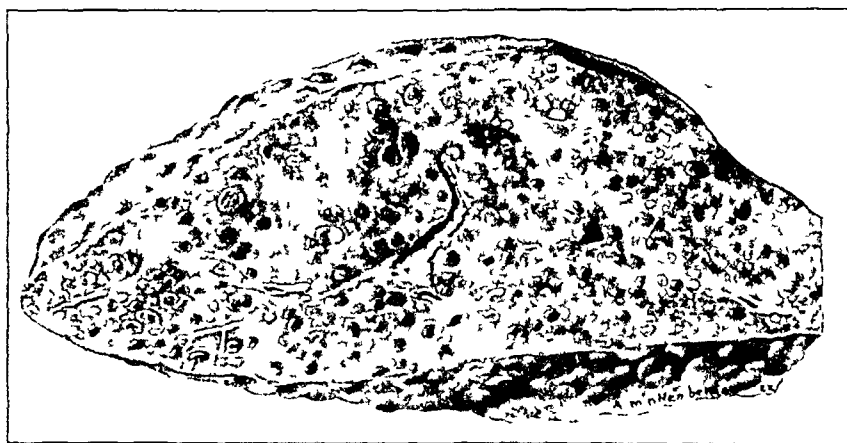


Fig 2—Cross section of liver showing the small islands of liver tissue and the greatly increased connective tissue between them.

The retention of salt and water increased in spite of the most rigid dietary restrictions. At times as little as 0.1 gm of sodium chloride was found in a twenty-four hour urine specimen, and the total urinary output was usually less than 500 cc. From time to time, usually in the morning, he vomited material containing food particles. Anemia increased slowly, but the yellow color of his skin became more marked.

Although it was evident that his general condition was deteriorating in spite of the temporary relief of symptoms afforded by repeated paracentesis, no marked change occurred until the morning of May 12, when he had a sudden attack of vomiting before breakfast. From this time on vomiting was persistent, and he suffered from distressing upper abdominal distention that resisted all efforts to relieve it. He became steadily weaker, and died in the morning of May 14.

*Additional Laboratory Findings*—Blood nonprotein nitrogen on March 8 was 25 mg per 100 cc, on March 29, 28 mg, postmortem, 91 mg (blood urea nitrogen, 21 mg). Blood sugar on March 8 was 116 mg per 100 cc. The urine gave no reactions for bile until three or four days before death. Plasma obtained at necropsy was distinctly bile stained, but the abdominal fluid contained no bile.

*Laboratory Examinations on Admission*—Radiographic examination of the chest and abdomen revealed right hydrothorax, the left side of the chest was clear, but the heart was displaced to the left, the splenic tumor gave a distinct shadow, but the liver did not appear to be enlarged. The blood count revealed red blood cells, 3,300,000, hemoglobin, 70 per cent, white blood cells, 6,100, polymorphonuclears, 65 per cent, lymphocytes, 28 per cent, large mononuclears,



Fig 1—Spleen above and liver below, showing the gross pathologic changes and the comparative size of the two organs

6 per cent, eosinophils, 1 per cent. Smear showed moderate achromia, there were no nucleated red cells nor basophilic stippling. The urine was light yellow and acid. The specific gravity was 1.019, there was no albumin or sugar. The sediment was negative. The Wassermann test was negative. Intracutaneous tuberculin ( $\frac{1}{50}$  mg) gave a positive reaction. The chest fluid and abdominal fluid were both sterile and of rather low specific gravity, with cells, pre-

In the spleen, the malpighian corpuscles were reduced in number, and some had about their periphery an accumulation of red blood cells forming a dense boundary. The sinuses were well filled with red and white blood cells and the fibrous reticulum was markedly increased.

The architecture of the liver was altered so that there were everywhere circular zones of cells surrounded by dense bands of connective tissue. The liver cells were granular and pale staining. They showed changes of degeneration, and in some areas were lacking in nuclei and had protoplasm that stained a homogeneous, pale pink. These cells were necrotic. In many zones the

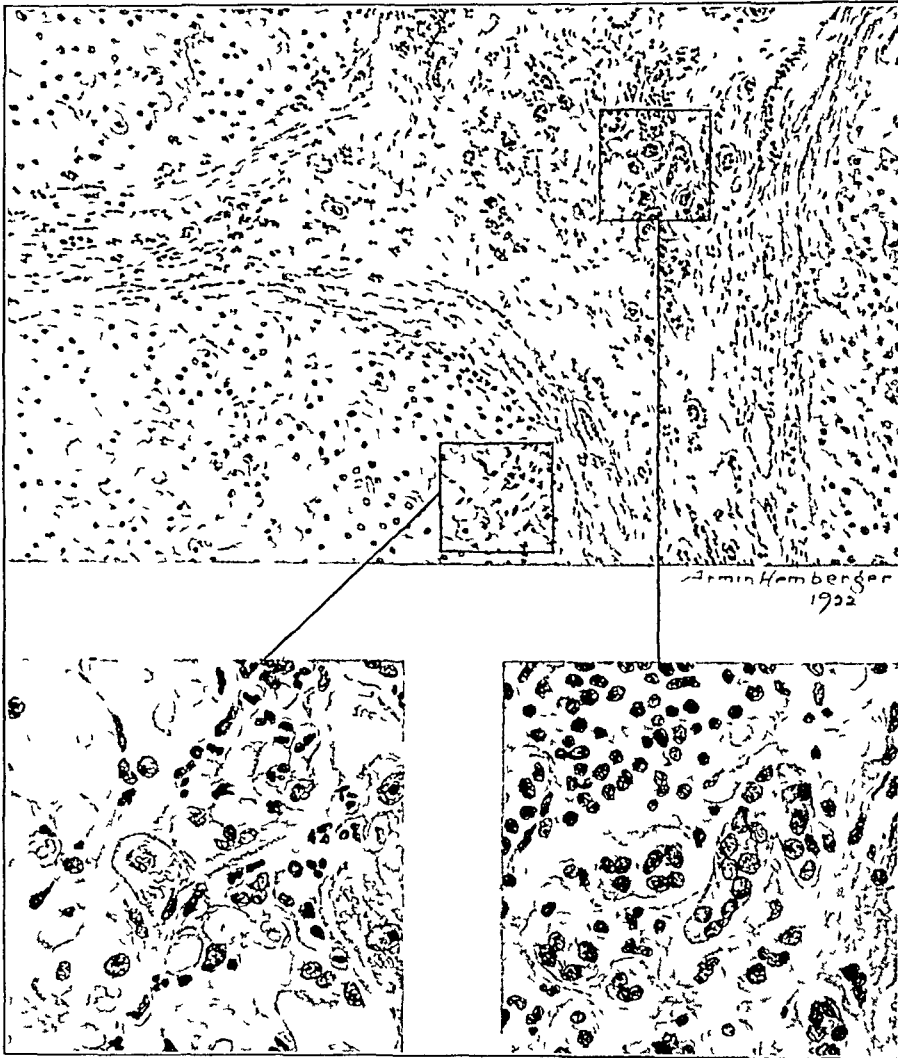


Fig 3—Microscopic sections of liver tissue, illustrating the loss of normal hepatic structure and the increase of fibrous tissue. The high power sections show the character of the degenerative changes in the liver cells, regeneration from the bile duct cells and the nature of the infiltration with both polymorphonuclear and mononuclear cells. There is no evidence of excessive pigmentation.

spaces between the liver cells were filled with polymorphonuclear leukocytes, and in several of the circular masses there were spaces left vacant by the disappearance of liver cells. These areas were filled with connective tissue. The fibrous tissue surrounding the liver cells was dense, and in it were many mononuclear cells and numerous bile ducts, some of which were in continuity with liver cells and appeared to be proliferating. In some zones polymorpho-

*Necropsy*—Because of restricted permission, necropsy was performed through a small abdominal incision. The organs, with the exception of the liver and spleen, were examined in situ and not removed.

The conjunctivae and the skin of the body were pale and had an icteric tint, but showed no pigmented lesions. The face, trunk and extremities appeared edematous. The abdomen was greatly distended, and the superficial abdominal veins were prominent. The peritoneal cavity contained approximately 2000 cc of clear, thin amber fluid. The vessels of the parietal peritoneum were enlarged and prominent. The abdominal contents appeared to be normally disposed. The lower pole of the spleen projected below the costal margin on the left side. The liver edge lay beneath the arch of the ribs. The stomach was moderately full, and the wall of the upper portion of the small intestine was dark. The right pleural cavity contained 500 cc of straw colored fluid. The left pleural cavity contained no excess of fluid. There were no adhesions on either side. In the pericardial sac there were about 25 cc of clear, pale fluid.

The heart was not removed, but appeared, as viewed through the abdominal incision, to be small and normal. The right lung, examined in the same way, appeared collapsed and atelectatic, the left lung was large, voluminous and crepitant.

The stomach contained a large amount of blackish red, grumous material. The vessels of the mucosa were injected. The duodenum contained bile and a quantity of material similar to that found in the stomach. The upper 6 feet (182.8 cm) of the small intestine contained material like that found in the stomach. The submucosal vessels were intensely injected in many places. Otherwise, neither small nor large intestines showed any abnormalities. The bile and pancreatic ducts joined and emptied at the ampulla of Vater, and were all patent. The pancreas was not removed, but section in situ revealed no gross changes in the organ.

The suprarenals showed no striking abnormalities.

The kidneys were not removed. They were of average size. On section, in situ, the capsules stripped readily, the markings were distinct, the cortex normal in thickness. The entire organs had a distinct yellowish green tint.

The spleen weighed 325 gm and measured 17 by 8 by 3 cm. It was firm and retained its shape after removal. The capsule was smooth. There were three small notches anterior to the proper hilus. On section it was firm, maroon in color, and the trabeculae were prominent. The cut surface was smooth, but did not protrude. The pulp was not excessive, and the malpighian bodies were not discernible.

The liver weighed 525 gm and measured 15 by 12 by 7 cm. Its surface was roughened by projecting, yellowish brown nodules which averaged from 3 to 4 mm in diameter. The capsule was thickened and wrinkled. The organ cut with resistance and the cut surface was everywhere marked by small yellowish green nodules from 3 to 4 mm in diameter, projecting from the surface and separated by grayish brown zones. Some of these nodules were definitely bile colored. The central veins were not prominent, and the destruction of liver lobules was not apparent. The striking changes were the hobnail appearance, the decrease in size of the organ, and the increase of connective tissue in all portions.

The gallbladder contained a small quantity of yellowish green bile, together with considerable tenacious mucus.

*Microscopic Notes*—The lungs, pleura, stomach, intestines, pancreas and suprarenals showed no remarkable abnormalities.

In the kidneys, the epithelium of the convoluted tubules was swollen and granular and the nuclei showed various stages of degeneration but the lumina of the tubules were free. The blood vessels of the glomeruli and the pyramids were well filled, and the tubules in the pyramids were unchanged.

tion of the oxidation tests revealed even larger amounts of melanin than were found on the first occasion and further investigation was undertaken a few days before the patient's death

Although the urine on some days was distinctly dark, there was little tendency to spontaneous oxidation at room temperature. The urine was highly colored with urobilin and some bile and showed a heavy precipitate of urates on standing. After only a few minutes on the steam bath, it became very dark, and a black precipitate slowly settled out. The addition of bromin water, ferric chlorid or nitric acid produced a similar precipitate. The precipitate formed after the addition of bromin water or nitric acid dissolved in carbonate solution, but could be reprecipitated by acidification with hydrochloric acid. It was difficult to obtain solution of the ferric chlorid precipitate because of the heavy precipitate of phosphates that was produced in the reaction. Solution and reprecipitation could be repeated indefinitely by the alternate addition of alkali and acid. The urine did not become dark after the addition of alkali, nor did it reduce alkaline copper solutions.

Several other urines have been subjected to the same treatment with entirely negative results. Among those chosen were specimens from (1) a patient with moderately advanced hypertrophic cirrhosis of the liver and ascites, (2) a patient with symptomatic purpura, venous thrombosis, compensated cardiac valvular disease and enlarged liver (this urine contained considerable urobilin), (3) a patient with carcinoma of the head of the pancreas and complete biliary obstruction, with a large liver, (4) a patient with carcinoma of the stomach, severe anemia and extensive metastases in the liver, (5) a patient with Banti's disease.

#### ISOLATION OF MELANIN

When it became clear that the material was undoubtedly melanin, an attempt was made to isolate it. As this was begun only three days before the patient's death, the amount recovered was not great. The method of isolation described by von Jacksch (precipitation by basic lead acetate, removal of the lead by filtration after treatment by hydrogen sulphid and evaporation of the filtrate) proved unsatisfactory.

In the urine of A. G., the patient with known melanotic sarcoma, the lead acetate removed the pigment, but it proved impossible to liberate it without great loss from the lead sulphid precipitate. The method finally employed consisted of (1) development of the color and concentration of the urine by partial evaporation on the steam bath, (2) precipitation by bromin water after acidification with concentrated hydrochloric acid, (3) recovery of the precipitate by centrifugalization, (4) repeated solution and reprecipitation in large centrifuge tubes by the alternate addition of strong sodium carbonate solution and concentrated hydrochloric acid (the latter added drop by drop until somewhat beyond the point of cessation of effervescence), (5) washing of the precipitate with 0.1 normal hydrochloric acid.

The first precipitation was always incomplete, the supernatant fluid remaining highly colored. Further concentration of the fluid yielded another precipitate. Even repeated concentration, however, failed to



nuclear leukocytes were found in great numbers in the tissue. There was fat everywhere in the form of small and large droplets. The central veins were not easily identified, and the hepatic artery, portal vein and bile duct usually found at the periphery were much distorted.

Stains for fat and iron on liver sections showed a great quantity of fat in the organs but essentially no iron.

The anatomical diagnosis was cirrhosis of the liver, chronic splenic tumor, ascites, hydrothorax, jaundice and hemorrhage into the stomach and duodenum.

For some time before his death the urine contained constantly large amounts of a chromogenic material that gave all the typical reactions of melanin. This was first discovered accidentally. The urine of another patient, A. G., suspected of advanced melanosa sarcoma, was tested for melanin. It gave typical

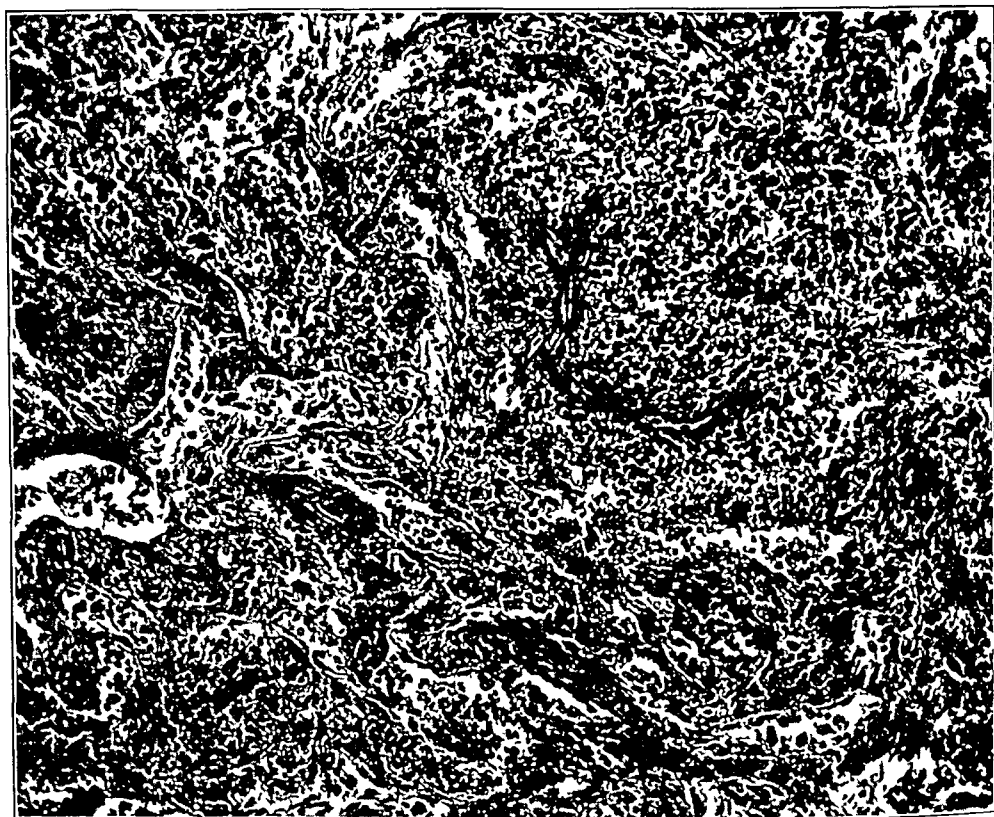


Fig. 4—Microscopic section from spleen

reactions after the addition of oxidizing agents, although it darkened only slightly when exposed to the air at room or icebox temperature. As a control, a specimen of urine from W. S. was exposed to the same oxidizing agents. The only reasons for choosing this specimen were that it was the most highly colored, concentrated urine at hand. After oxidation with bromin water and with ferric chlorid a definite black precipitate formed, which was almost as marked as that formed in the urine of the patient suspected of melanosa sarcoma. It seemed so inconceivable that W. S. could be excreting melanin that the only immediate result of this observation was to cast doubt on the specificity of the tests.

An exploratory operation, however, confirmed the diagnosis of melanosa sarcoma with extensive metastases in A. G. Shortly after this it was noticed that on some days W. S.'s urine became distinctly dark on standing. Repeti-

was quite similar to that of the alkaline solutions. Spectroscopic examination of the solutions revealed no absorption bands in the visible spectrum.

## COMMENT

So far as we have been able to determine, this is the first case in which melanuria has been reported as occurring in a person who showed no evidence of the presence of a pigmented tumor. What is perhaps more remarkable is the fact that none of the important viscera showed any abnormal pigmentation of the melanotic type. The patient was of the black haired, dark skinned type, indicating a natural tendency to pigmentation, but the skin revealed no localized areas of excessive pigment deposition. There was nothing in the chemical analyses of the urinary pigment that differentiated it from other specimens of melanin.

The striking pathologic lesion discovered at necropsy was an extreme reduction of liver substance, apparently due to a destructive inflammatory condition which the patient had survived long enough to permit considerable repair and connective tissue replacement. Unless we except the melanuria, there is nothing in the clinical or pathologic picture that cannot be adequately accounted for on the basis of such a lesion alone. The question may reasonably be raised whether the melanuria was not also dependent on the hepatic lesion.

Eppinger,<sup>1</sup> in an extensive review of the subject, claims that the mere presence of a melanotic sarcoma in the body, no matter how extensive, will not produce melanuria. Melanin, he says, appears in the urine only after the liver has been extensively invaded by metastases. He argues from this that the normal liver breaks down melanin that escapes into the circulation. Only when the liver is injured sufficiently to impair its ability to destroy melanin does the latter appear in the urine. It is conceivable that some of the melanotic pigments that produce the normal coloration of a dark person might find access to the blood and, in the absence of normal liver function, fail to be destroyed and thus pass into the urine. This could, however, hardly account for the melanuria in this case, because the quantities of pigment recovered were too great. The amount obtained in three days was more than 1 gm., the total estimated amount of coloring matter found in the skin and hair of a dark negro. In spite of the negative clinical and pathologic findings, an excessive production of melanin must be assumed, the source of which remained undiscovered.

The case is of interest because it indicates that melanuria can occur in the absence of melanotic sarcoma. If investigation of similar cases reveals the same condition, a new light may be thrown on the metabolism of this interesting group of pigments.

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<sup>1</sup> Eppinger. *Biochem Zehnschr* **28** 181, 1910

remove all the color from the original fluid. Some color was apparently lost in the first reprecipitation also. After the second reprecipitation, however, the supernatant fluid came away practically clear. With the first precipitate a large admixture of acid salts was obtained. These were washed out and carried away in subsequent precipitation. It was later found that repeated washing of the first precipitate with 0.1 normal hydrochloric acid hastened this process. The first precipitation, however, was more complete in highly acid solutions.

Because of the relatively small amount of urine available, no attempt was made to obtain the unoxidized melanogen by the method of Eppinger. It seemed safer to try for the melanin alone, because the latter by its color afforded constant evidence of its presence and an indication of the efficiency of the methods employed for its recovery.

An analysis of the material was made by Miss R. B. Hubbell in the department of physiological chemistry. The complete report of her studies will be published elsewhere. These studies, however, confirmed our findings. The pigment gave all the usual reactions for melanin. For comparison, a sample of melanin made from black hair and a small amount obtained from the urine of A. G. were also analyzed. The results for nitrogen, ash, and sulphur are shown in the table.

*Results of Analyzing Melanin from Black Hair and from Urine*

Sample	Nitrogen (Ash-Free)	Ash	Sulphur	Iron
From hair	12.80	1.60	2.50	0
W. S.	11.00	11.90	2.21	0
A. G.	8.72	3.34	—	0

The amounts of nitrogen and sulphur were quite comparable to those obtained from the sample of prepared melanin and agree with analyses of melanin found by others in urine from patients with melanotic sarcoma. The nitrogen in the sample from A. G. was considerably lower. The sulphur content was also quite typical. On the other hand, the ash from the W. S. sample was very high. This may well be due to impurity. The amount of material available was not sufficient to permit attempts at further purification.

A study of the solubilities of the pigment gave some rather interesting results. Besides the ordinary solubilities which are described as the characteristic properties of melanin, the material from W. S. also showed some distinctive atypical solubilities. It dissolved freely in amyl alcohol and to a lesser extent in butyl alcohol and ethyl alcohol. The specimen obtained from hair proved insoluble in all these solvents, and the sample from A. G. was only slightly soluble in butyl alcohol and insoluble in amyl and ethyl alcohol. The color of these solutions

and, in fact, on such a great variety of bodily activities that the condition of the heart itself may be entirely obscured and gravely erroneous conclusions reached

Since the advent of the electrocardiograph, attempts have been made to correlate the findings of abnormal deflections in electrocardiographic tracings with definite pathologic conditions of the heart muscle. While data on this particular point are still in the process of being formulated, we may safely say that certain of these abnormal deflections are coming to be regarded more and more as indicative of myocardial damage.

The two groups of deflections which have been particularly regarded with significance are the Q-R-S group and the T-waves.

The Q-R-S group normally should not exceed one-tenth of a second in duration, and in a tracing that shows a longer duration we are justified in assuming that there is defective conduction through one or the other ventricle. Again, a notching of the Q-R-S group in leads other than Lead III has come to be regarded as additional evidence of myocardial damage. Occasionally we find this abnormal width of the Q-R-S group associated with a notching or slurring of the waves. The conduction system is regarded as specialized heart muscle, and constitutes only a small percentage of the total heart muscle tissue. We know that it may be disturbed functionally without necessarily being organically damaged. In cases in which the conduction system shows this evidence of persistent impairment, it does not necessarily follow that the rest of the cardiac muscle is also impaired.

Nevertheless, in many cases, organic disease of the heart is an accompaniment of a defective conduction system. The heart may recover from widespread infection, leaving some residual scar tissue. If this should happen to be in some part of the conduction system, we may get rather startling electrocardiograms in an otherwise normal person. It would seem rather infrequent, however, for this relatively small area of the heart to be damaged without affecting other areas in the myocardium.

The other group of deflections which have come to be regarded as giving us some information concerning the state of the myocardium are the T-waves. Normally these waves are upright, although occasionally in Lead III we may find them inverted, and an inversion of the T-wave in Lead III is usually regarded as of no particular significance. However, an inversion of the T-wave in Lead I or II, or both, or in all three leads, cannot be disregarded. The association of these abnormal deflections, in leads other than Lead III, with definite myocardial damage, has now been demonstrated sufficiently often to render their occurrence in a given case a rather bad omen.

# THE VALUE OF THE ELECTROCARDIOGRAPH IN PROGNOSIS

W A BLOEDORN, A M, M D  
Lieut Commander (M C) U S Navy

AND

L J ROBERTS, M D  
Lieut (M C) U S Navy ,

WASHINGTON, D C

The electrocardiograph has definitely established itself as an invaluable aid in the diagnosis of the arrhythmias. In this respect, it is universally admitted that it is superior to the polygraph. As a rule, electrocardiographic tracings give us a clear-cut picture of the mechanism of the heart, the spread of the excitation wave and the presence or absence of an abnormal rhythm.

The additional data made available through electrocardiographic studies can be applied clinically with great advantage to both the patient and the physician. With this additional knowledge that the electrocardiograph has placed in the hands of the physician, he is able in most instances to make the correct diagnosis of an arrhythmia by physical examination alone. Nevertheless, when any question arises regarding the precise mechanism of the heart, the electrocardiograph becomes the court of last resort.

Within the last few years, as the result of innumerable tracings and the researches of many investigators, the electrocardiograph has come to be regarded as having some additional value to the clinician in the way of prognosis. As prognosis constitutes one of the most important aspects of a cardiac case, any measure which may throw additional light on this vital matter should be utilized as a routine procedure.

We are able with a fair degree of certainty to diagnose by clinical means the state of the various valves of the heart. The condition of the conduction system of the heart at any given time can be determined by the electrocardiographic tracing. But even knowing the state of the valves and of the conduction system, we are still left more or less in the dark as regards the condition of the cardiac muscle itself, which, after all, is probably most important in the vast majority of cardiac cases.

We have attempted to devise functional tests which will give us information regarding the state of the cardiac muscle. The great number of these tests proposed is in itself evidence that no test is entirely satisfactory. Each of the various tests devised depends for its result not only on the integrity of the heart muscle but also on the nervous mechanism, the respiratory apparatus, the state of the blood

standpoint of prognosis and justifies the use of the electrocardiograph as a valuable clinical adjunct

Wilson states that when the T-wave is completely inverted in Lead I or II and the patient has had no digitalis, cardiac diseases may be diagnosed with a fair degree of certainty even when the Q-R-S group is normal

As illustrating the type of patient to which we refer, a case is reported, with electrocardiographic tracings and postmortem findings

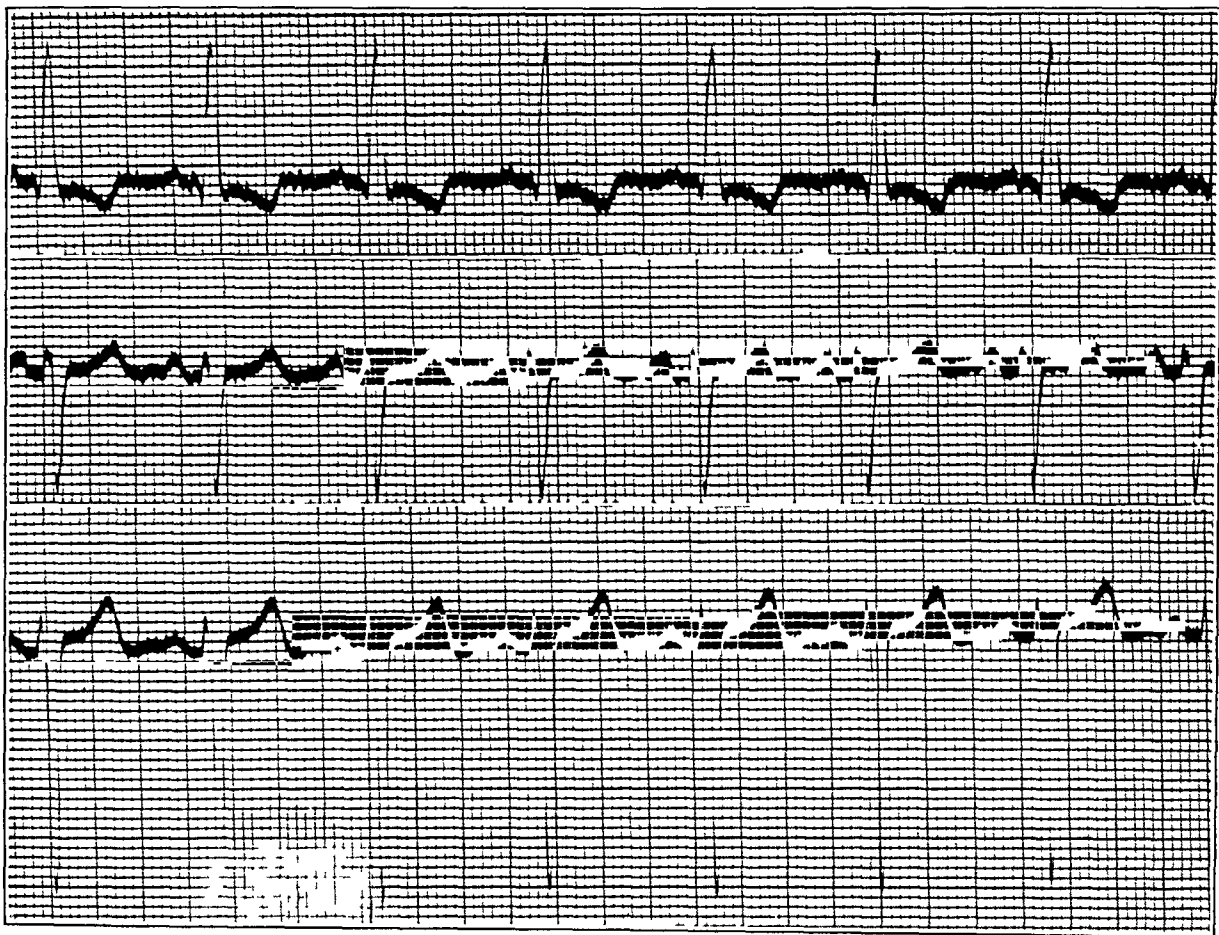


Fig 1—T-wave in Lead I is inverted, and there is some increase in the Q-R-S interval Time in fifths and twenty-fifths of a second

#### REPORT OF A CASE

*History*—A man, aged 71, had been in excellent health until within a few months before examination He complained of some shortness of breath on exercise, although not sufficient to incapacitate him to carry on his duties, which were largely of a supervisory character and involved little physical exertion

*Examination*—Physical examination revealed a rather marked tortuosity of the superficial arteries and the retinal arteries, which showed evidence of sclerosis The blood pressure was systolic, 212, diastolic, 112 There was a blowing systolic murmur over the apex, and the aortic second sound was rather loud and ringing in character Occasionally there was a reduplication of the second sound at the base

It must be kept in mind, however, that the heart is able in many instances to recover from the effects of toxins or bacterial invasion and that one must exercise great care in invariably giving a bad prognosis, even when definite signs of myocardial injury can be demonstrated

It is well known that the best cardiac drug in our possession, namely, digitalis, may produce significant changes in the electrocardiographic tracing, such as an inverted T-wave and a definite prolongation of the conduction time. Yet no one would go as far as to say that digitalis produces a myocarditis, and we see that when the drug is discontinued these changes in the tracing eventually disappear.

The same thing may be said of the acute infectious diseases. The heart may become involved during the course of these diseases and a definite myocarditis produced with significant changes in the electrocardiogram, and it is well for the cardiologist to exercise some self-restraint in giving his prognosis, even though it may be backed up by significant abnormalities in the electrocardiogram. It is not unusual for these abnormalities to disappear entirely as the patient recovers and the heart gradually regains its normal capacity. Nevertheless, these abnormalities occurring in any given case should serve to focus attention on the heart, and the patient in every instance should have careful supervision, adequate rest and a routine tending to safeguard the heart until it has regained its normal functional capacity.

It is in cases in which these abnormalities in the electrocardiogram persist that we feel more at liberty in using the tracing for prognostic purposes. Their prognostic import becomes all the more significant in those cases in which the history of acute illness is absent or remote, and in which the symptoms of heart failure come on suddenly as in an anginal attack, or insidiously as in the common type of chronic myocarditis.

The lesions most frequently found associated with this abnormality of the electrocardiogram are probably hypertension, chronic myocarditis, arteriosclerosis, angina pectoris, hyperthyroidism, chronic nephritis and disease of the coronary artery. The outstanding cardiac lesion in the majority of these cases is usually a fibrosis replacing and encroaching to some extent on the cardiac muscle.

A normal electrocardiogram, on the other hand, can never be regarded as indicating a perfectly healthy myocardium.

Pardee and Master state that ventricular muscle disease is a far more important deduction from the finding of abnormal ventricular waves than it has been heretofore considered, so that the clinical importance of abnormal electrocardiograms becomes more apparent.

Willius states that significant T-wave negativity and an abnormal Q-R-S complex in all derivations is of the greatest value from the

*Necropsy*—The postmortem examination of the heart by Lieut R M Choisser, M C, U S Navy pathologist at the Naval Medical School, revealed that the heart was large (600 gm) for the size of the person. The epicardial fat was yellowish and normal in amount. The superficial vessels were prominent and distinctly tortuous. The coronary arteries were sclerosed and non-compressible. Their outline was irregular because of the deposition of calcareous material. The anterior coronary artery when opened showed the lumen narrowed throughout by sclerosis and calcium deposits. In the descending branch, at a distance of 11 cm from its origin, the lumen became distinctly narrow and was completely occluded by a large calcareous plaque. No gross lesions were demonstrable in the myocardium below this point. The lumen of the posterior coronary artery was also similarly narrowed throughout its course. It showed in its descending branch, 5 cm from its origin, a definite narrowing,

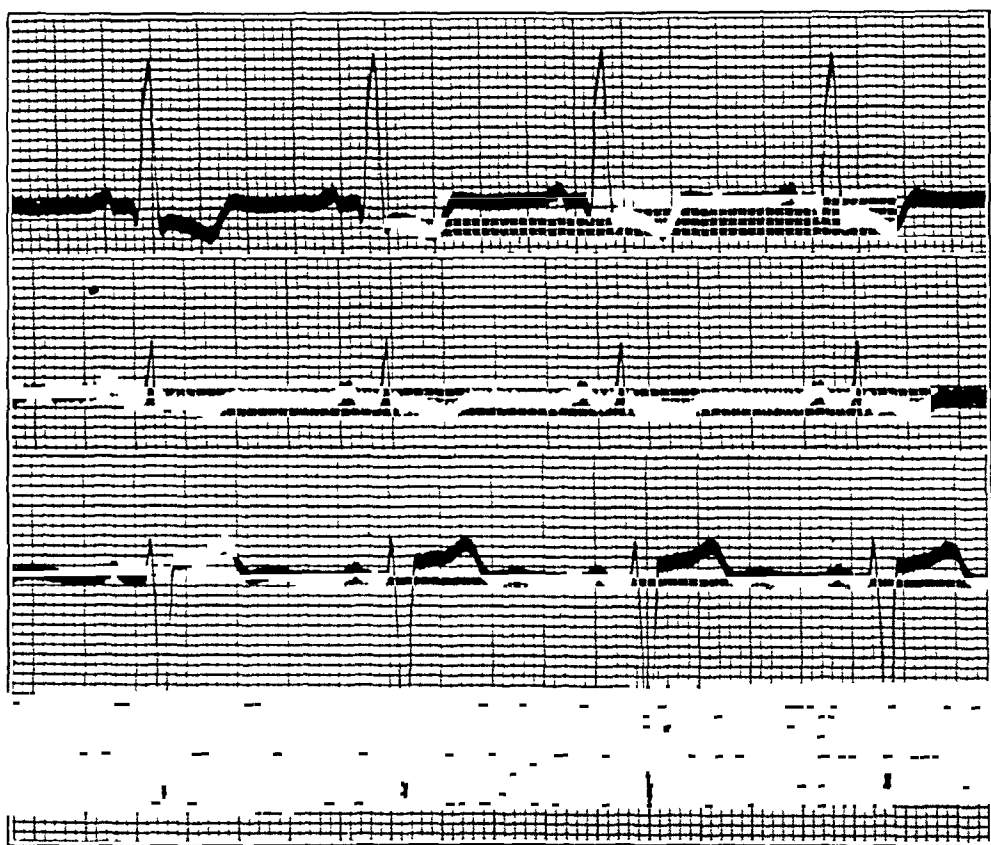


Fig 3—Inversion of the T-wave in Leads I and II. The Q-R-S interval is 0.12 seconds. The tracing was taken ten days before the death of the patient.

which amounted to almost an occlusion. The tricuspid valve measured 12 cm. The right ventricular wall was brownish and 11 cm in thickness. The pulmonary artery showed a few areas of atheromatous changes, normal cusps and valve measurement of 6 cm. The left auricle was normal, with a wall measurement of 7 cm. The myocardium of the left ventricle was light brown with whitish areas of fibrous tissue throughout, it was markedly hypertrophied, being 2 cm in thickness. The aorta showed atheromatous changes and plaques of calcium deposit. The valve measured 7 cm.

On microscopic examination of the coronary arteries, the media showed little change in structure, although its outline was irregular because of the protruding structures below. The intima was markedly thickened and irregular. Fibrosis was marked, and some areas showed an accumulation of small round cells. A calcareous deposit was seen throughout. In the places in which



The Wassermann reaction was negative, the urine showed albumin and granular casts and the blood showed a nonprotein nitrogen of 45 mg

The electrocardiograph at this time showed a rapid rate which was quite regular. There was marked left side preponderance. The P-R interval was normal. The P-waves were upright and normal in appearance in the three leads. The Q-R-S interval exceeded one tenth of a second and could therefore be said to be definitely prolonged. The T-wave was inverted in Lead I. Figure 1 contains the electrocardiograms taken at this time. Eighteen days later the electrocardiogram showed no essential change from previous tracings except for a brief period of extrasystoles arising in the right ventricle and occurring at every other beat. Figure 2 contains these tracings. Two weeks after the

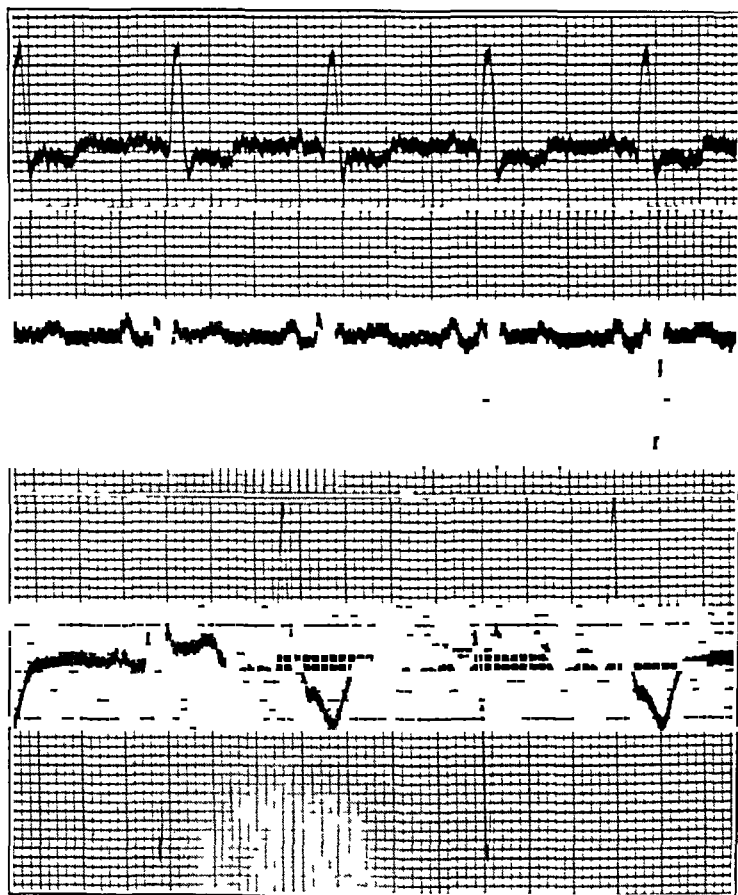


Fig 2—A brief period of extra systoles arising in the right ventricle. The inversion of the T-wave in Lead I and the increased Q-R-S interval persist

second electrocardiogram was taken a third electrocardiogram showed that the resistance was 1,800 ohms, the rate 62 and regular, the P-wave upright and normal in the three leads, the P-R interval 0.18 seconds, there was left side preponderance and notching of the S-wave in Lead II, the Q-R-S interval was 0.12 seconds, the T-waves were inverted in Leads I and II, upright in Lead III, following exercise the rate became 95 and one premature contraction arising in the auricle was seen, and after two minutes' rest the rate was 72. Figure 3 shows the tracings taken at this time.

*Course of Illness*—In view of these findings, together with the result of the physical examination, a grave prognosis was made. The patient, however, refused to remain in bed and went about his duties as usual. Ten days after the third electrocardiogram was taken, the patient died suddenly.



Fig 5—Photomicrograph of a section of the left ventricle below the point of occlusion of the anterior coronary artery, showing marked fibrosis and replacement of muscle cells by connective tissue

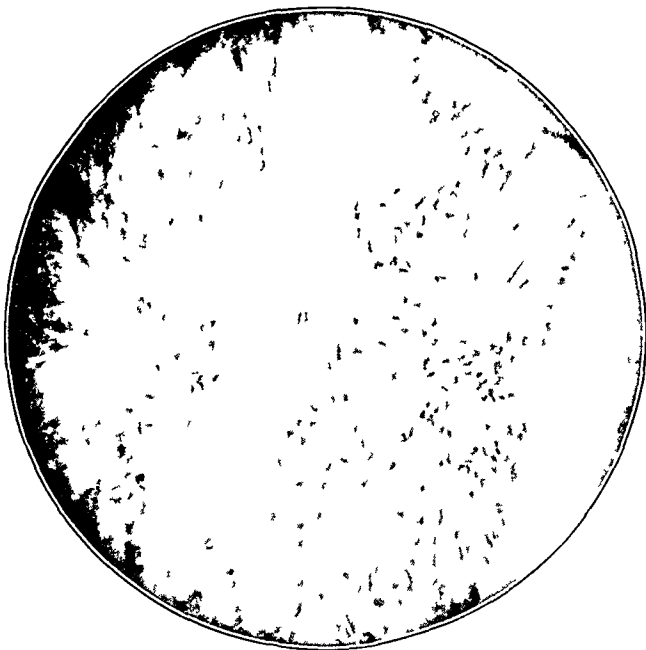


Fig 6—Photomicrograph of the anterior coronary artery, showing a marked calcareous deposit with thickening of the intima and with fibrosis

extreme narrowing occurred, it appeared to be all that remained of the original coat. The adventitia was thickened, consisting entirely of dense bands of fibrous connective tissue.

The myocardium of the auricles showed a degeneration of some of the muscle fibers and a slight amount of brownish pigmentation in the cytoplasm of the cells. Short bands of fibrous tissue lay between the muscle fibers and in



Fig. 4—Heart showing tortuous and sclerosed anterior coronary artery. At the point enclosed by the circle, the lumen was practically occluded by a calcareous plaque.

places in which degeneration had taken place. The ventricles, especially the left, showed diffuse degenerative changes and marked fibrosis. In the region below the occlusion of the anterior coronary artery, the muscle cells appeared to be almost completely displaced by connective tissue. The cytoplasm of the remaining muscle cells showed a brown granular deposit. The vessel walls were quite thick and sclerosed throughout.

# EXPERIMENTAL INFECTIOUS STREPTOCOCCUS ENDOCARDITIS AND ITS ARSENICAL THERAPY (SODIUM CACODYLATE)

J A BARGEN, M D

The John Jay Borland Fellow in Medicine  
CHICAGO

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## DEFINITION

Names have been introduced at various times descriptive of the pathologic changes occurring in heart valves following bacterial infections. Such names as simple acute endocarditis, benign, infectious, bacterial, chronic, malignant, septic and ulcerative endocarditis and more recently endocarditis lenta and subacute bacterial endocarditis have been suggested by clinicians. Litten,<sup>1</sup> in 1900, classified infections of the heart valves into acute, malignant and chronic, by the first two meaning infections causing in patients severe septic symptoms and death in a short time, by the last one mentioned those less severe and of much longer duration. Litten's classification prompted a lively discussion regarding septic or malignant endocarditis referred to by the early writers. Simons<sup>2</sup> prefers the term "bacterial endocarditis," a designation more accurate than "malignant," "septic" or "ulcerative." Libman<sup>3</sup> prefers the names "subacute bacterial endocarditis" (replacing the word "bacterial" by "streptococcus" or the name of such other organism as may be the causal agent) for all such infections continuing at least six weeks. The clinical designation of this disease seems to be

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\* Work done in the Pathological Laboratory of St. Luke's Hospital

1 Berl klin Wchnschr **36** 609, 1899

2 Quart J Med **7** 291, 1914

3 Libman, E. Characterization of Various Forms of Endocarditis, J A M A **80** 813 (March 24) 1923

The diagnosis was arteriosclerosis of the coronary arteries with complete occlusion of the descending branch of the left anterior by calcareous plaques, 11 cm from its origin, sclerosis of the right posterior with partial occlusion of the descending branch, 5 cm from its origin, marked hypertrophy of the heart associated with chronic interstitial myocarditis and brown atrophy, and atheromatous changes in the pulmonary artery and bulbus aortae

#### COMMENT

It would appear, in view of the postmortem findings in this case, that the inversion of the T-waves in Leads I and II and the widening of the Q-R-S group were the result of grave myocardial disease, and that their persistence justified one in giving a grave prognosis

#### SUMMARY

1 The ability of the clinician to diagnose valvular disease of the heart and lesions of the conductive system is well established

2 If data can be obtained whereby we can more frequently detect myocardial damage, a more accurate prognosis can be made

3 Evidence has been accumulating that electrocardiograms showing persistent straddling or splitting of the Q-R-S complex and inversion of the T-waves in Leads I and II are indicative of myocardial damage

4 A case is reported in which electrocardiograms were obtained illustrating the presence of a prolonged Q-R-S complex, notching of the S-wave in Lead II and inversion of the T-wave in Leads I and II. A diagnosis of damaged myocardium was made and a bad prognosis given. Sudden death of the patient occurred within four months and postmortem examination of the heart revealed chronic interstitial myocarditis and marked coronary sclerosis, with occlusion of the descending branch of the left anterior coronary artery

5 The association of the foregoing abnormalities of the electrocardiogram with definite myocardial and coronary damage, with resulting early death, appears to strengthen the belief that these findings justify a bad prognosis, particularly if they persist

6 These abnormalities of the electrocardiogram are usually accompanied by other signs of a failing myocardium, but in certain cases may be the only evidence demonstrable

## EXPERIMENTAL OBSERVATION BY OTHERS

Experimental studies of heart valve infections are comparatively few, clinical references many. In 1914, Simons<sup>2</sup> published an excellent review of the clinical literature up to that time, and in 1917 Kinsella<sup>15</sup> published a similar review including nearly all of Simon's references.

In 1885 a chronic septicemia was produced experimentally for the first time by Philopowicz and Wyssokowitch<sup>16</sup>. They found an endocarditis in rabbits after the intravenous injection of pure cultures of bacteria. Wyssokowitch<sup>16</sup> observed such infections frequently if he injured the heart valves or endocardium by sounding one of the carotid arteries before the intravenous injection of bacteria. In the same year, Ribbert<sup>17</sup> produced tricuspid endocarditis by the injection of bacterial suspensions prepared from growth on potato medium. Numerous attempts have been made to discover the fate of bacteria injected intravenously into animals, beginning as early as 1874 with the experiments of Traube and Gescheidlen<sup>18</sup>. Bull,<sup>19</sup> seems to express best the essential results of such experiments. He believes the virulence of bacteria (streptococci and pneumococci) injected intravenously determines the fate of the host. If the streptococci are virulent, the animal (rabbit) dies within six days, whereas a less virulent strain produces a chronic infection somewhere in the body.

Allison<sup>20</sup> produced streptococcus septicemia in forty-six rabbits with *Streptococcus hemolyticus* and *Streptococcus viridans* recovered from patients with puerperal sepsis, mastoiditis, from normal and infected throats and from patients with other diseases in which bacteria were present in the blood. He found in these experiments that the course of such septicemias, experimentally produced, depends on several factors, such as the virulence of the bacteria injected, the native agglutinating power of the rabbit serum and the phagocytic property of the leukocytes. If the organisms are not virulent enough to cause death at once or within a few hours after injection, they disappear rapidly from the circulating blood and accumulate in the capillaries and venous sinuses of the viscera. After a time the bacteria reappear in the circulation and cause a rapidly fatal septicemia or localize in some organ from which repeated "showers" of bacteria appear in the blood stream.

15 Kinsella, R. A. Bacteriologic Studies in Subacute Streptococcus Endocarditis, Arch. Int. Med. **19** 367 (March) 1917.

16 Philopowicz and Wyssokowitch. Ztschr. f. Hyg. u. Infektionskrankh. **1** 3, 1886.

17 Ribbert. Deutsch. med. Wchnschr. **11** 717, 1885.

18 Traube and Gescheidlen. Jahresbericht d. Schlessischen Gesellschaft Vaterland, Culture, 1874.

19 Bull. J. Exper. M. **22** 475, 1915.

20 Allison. J. M. Res. **38** 55, 1918.

best expressed by the terms "subacute" or "chronic infectious endocarditis," and where the causal bacterium has been demonstrated, its specific relation expressed by including in the name a significant term, for example, chronic infectious streptococcus endocarditis

#### ETIOLOGY

Virchow,<sup>4</sup> in 1855, suggested the etiologic relationship between bacterial infections of the uterus and valvular endocarditis. This is the first mention of a sequence of infections which now generally is believed to exist, that is, valvular endocarditis is secondary to some primary focus of infection elsewhere in the body. A series of reports between 1887 and 1899 by Weischelbaum,<sup>5</sup> Frankel,<sup>6</sup> Sanger and Harbitz,<sup>7</sup> mention the specific bacteria associated with malignant or septic endocarditis and include streptococci, staphylococci, and gonococci. By developing methods and technic for culturing the blood of patients, Sittman<sup>8</sup> thoroughly established this aid in diagnosing chronic infectious endocarditis, although previous sporadic attempts had been made by others to culture bacteria from the blood of patients suspected of having endocarditis. Later refinements by Kraus,<sup>9</sup> Gravitz,<sup>10</sup> Kuehnau,<sup>11</sup> Lenhartz<sup>12</sup> and Canon<sup>13</sup> further emphasized the importance of culturing the blood.

Although bacteria such as streptococci, staphylococci, gonococci, pneumococci, Friedlander's bacillus and *Bacillus influenzae* have been isolated from the blood of patients with endocarditis and also from the diseased heart valves at postmortem, the organism most frequently found in such infections is a coccus, variously termed *Streptococcus viridans*, *Streptococcus mitis*, *Streptococcus tenuans* or simply an endocarditis coccus. Some clinicians such as Simons<sup>2</sup> and Billings,<sup>14</sup> choose to place the organism in the streptococcus-pneumococcus group without further classification. All observers agree that the organism is a gram-positive coccus of low virulence, producing green on human blood agar and at some time growing in chains.

4 Virchow. Gesammelte Abhandlungen, 1855

5 Weischelbaum. Centralbl f Bakteriöl 2 209, 1887

6 Frankel. Virchows Arch f path Anat u Physiol 108 286, 1887

7 Sanger and Harbitz. Deutsch med Wchnschr 25 121, 1899

8 Sittman. Deutsch Arch f klin Med 53 323, 1894

9 Kraus. Wien klin Wchnschr 8 472, 1895

10 Gravitz. Charite-Ann 19 154, 1894

11 Kuehnau. Ztschr f Hyg u Infektionskrankh 25 492, 1897

12 Lenhartz. Munchen med Wchnschr 48 1123 and 1157, 1901

13 Canon. Mittheilungen aus den Grenzgebieten 10 411, 1902

14 Billings, F. Chronic Infectious Endocarditis Arch Int Med 4 409 (Nov.) 1909

Various antiseptics have been injected intravenously, such as collargol and eusol, in the hope of establishing some specific therapeutic agent. Arsenic in various forms has been used but in no systematic way. Recently Capps<sup>27</sup> reported the clinical progress of eight patients with *Streptococcus viridans* endocarditis treated by the intravenous injection of sodium cacodylate. Four of these patients were apparently well after three, five, six and twelve years, respectively, which affords

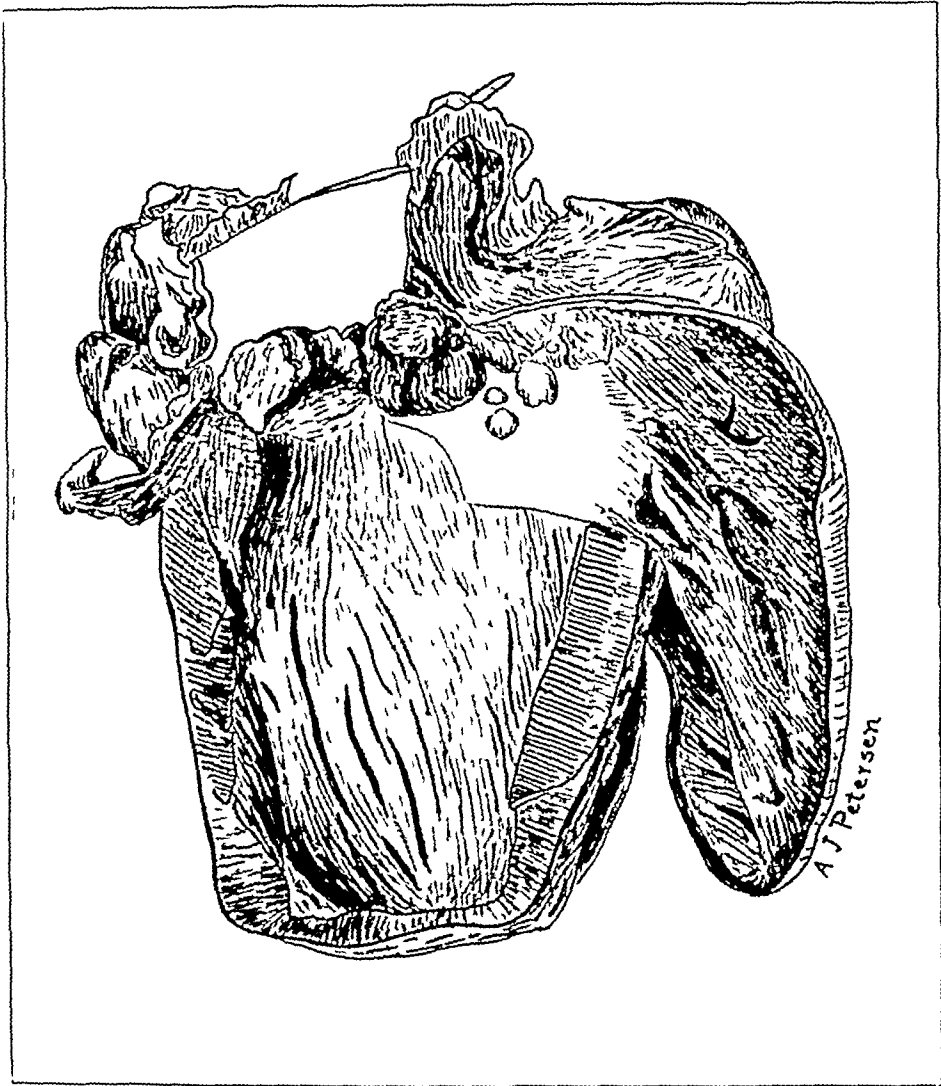


Fig 1—An extensive thrombo-ulcerative aortic endocarditis

some hope from arsenical therapy. Since his first report, Billings has also had several patients who recovered under treatment with sodium cacodylate.

Sodium cacodylate has been given in various diseases, usually by mouth, but also hypodermically and intravenously. Peyre<sup>28</sup> has

<sup>27</sup> Capps. Am J Md Sc 40 165 (Jan) 1923

<sup>28</sup> Peyre. Presse méd 27 615, 1919



When tissue reactions are sufficient to combat the bacteria the animal slowly recovers

Rosenow<sup>21</sup> has emphasized that many bacteria localize specifically in certain tissues of the body, and such terms as "specificity," "selective action" or "elective activity" have been suggested to designate this affinity

In an effort to find some drug which might be efficacious in the treatment of valvular endocarditis, Allison<sup>20</sup> used experimentally arsenical preparations, such as different brands of arsphenamin. He observed that the mortality in rabbits with experimental septicemias treated with these arsenicals was 30 per cent less than a corresponding group which received no treatment

#### MORTALITY REPORTS

The death rate of patients with chronic infectious endocarditis is high. Osler,<sup>22</sup> reporting the clinical results of ten patients, mentions a 100 per cent mortality. Billings<sup>14</sup> observed one of fourteen patients recover, Horder<sup>23</sup> one of 150, and Libman<sup>24</sup> five of 146. Libman's five patients when mentioned in a report in 1923 had been well nine, seven, five and two years, respectively. Oille, Graham and Detweiler,<sup>25</sup> have reported a series of twenty-three patients with positive blood cultures and a diagnosis of "subacute bacterial endocarditis" in which they gave a hopeful prognosis, but as none of these patients had been followed for more than a year, and since the disease is chronic it is presumptive to record them as having recovered.

Clinicians usually regard this disease as fatal.

#### SPECIFIC THERAPY

Numerous attempts have been made to find a specific therapy for active infectious endocarditis. Autogenous vaccines, serums, blood transfusions, and drugs introduced into the system for the purpose of destroying or attenuating the bacteria have been tried. Horder,<sup>23</sup> in a large experience, has failed to observe any benefit from serums and blood antiseptics.

Autogenous vaccines and antistreptococcic serums have been used extensively by Billings<sup>14</sup> and Jochmann,<sup>26</sup> but with no definite results.

21 Rosenow. *J Infect Dis* **6** 245, 1909, **7** 411, 1910, **11** 210, 1912, *New York State M J* **12** 441, 1912.

22 Osler. *Quart J Med* **11** 219, 1909.

23 Horder. *Quart J Med* **11** 289, 1909.

24 Am J M Sc **144** 313 (Sept) 1912. Also Footnote 3.

25 Oille, J. A., Graham, D., and Detweiler, H. K. *Streptococcus Bacteremia in Endocarditis. Its Presence Before and During the Development of Endocardial Signs*, *J A M A* **65** 1159 (Oct 2) 1915.

26 Jochmann. *Berl klin Wchnschr* **49** 436, 1912.

infectious endocarditis, (2) the influence of sodium cacodylate on the clinical course and the healing process of endocardial infections in rabbits

*Methods*.—Various methods of blood culture were employed. Rosenow's<sup>30</sup> anaerobic tubes were used constantly, modified slightly, using an 0.8 per cent agar and ascitic fluid with the sediment of blood centrifuged at high speed and sealed with paraffin. The tubes were controlled by plates of the same materials. The modification of the

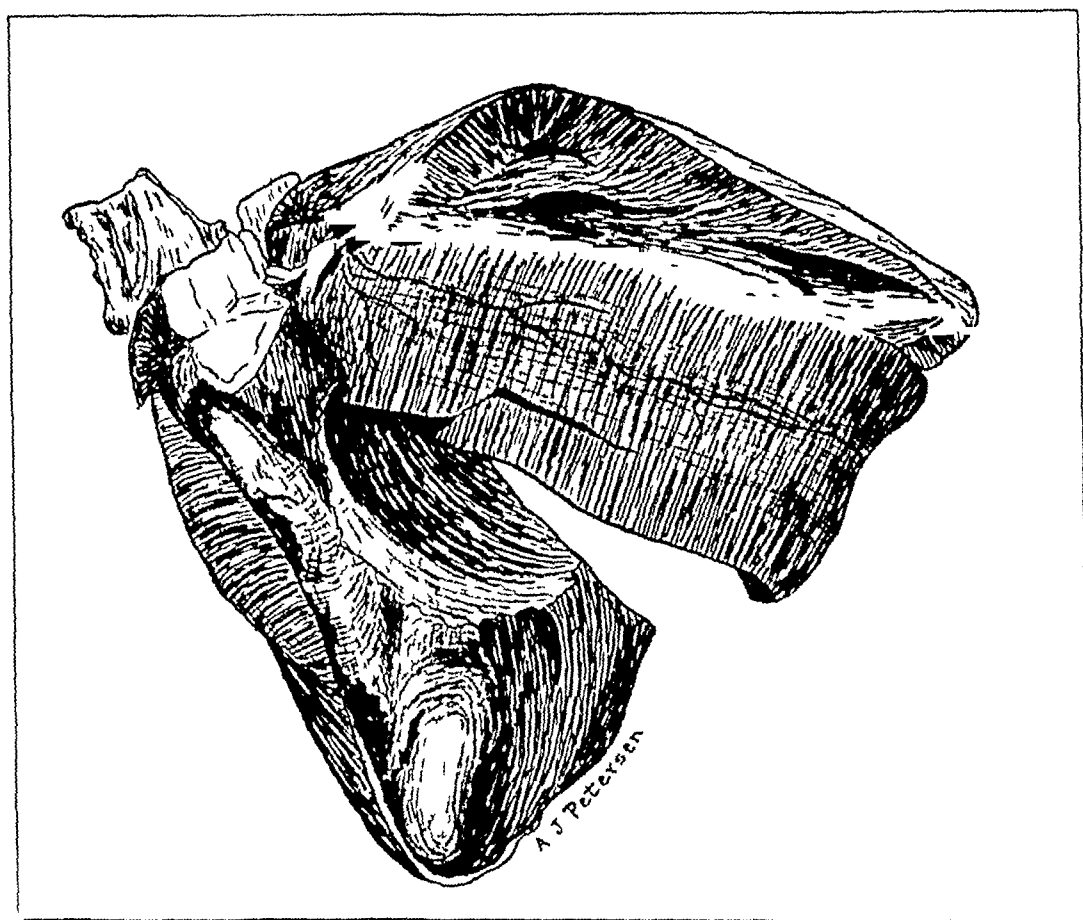


Fig. 3—An extensive thrombo-ulcerative tricuspid and mural endocarditis

Rosenow tubes consisted in using a tall tube, plugged with cotton at one end and a cork stopper at the other, the advantage being that the tube need not be broken to remove colonies of bacteria from the column of agar. The Noguchi<sup>31</sup> anaerobic tubes with a 0.5 per cent agar and citrated blood to fill half of a tube and when solidified covered by the same quantity of Ringer's solution, blood serum and

<sup>30</sup> Rosenow, E. C. The Newer Bacteriology of Various Infections as Determined by Special Methods, *J. A. M. A.* **63** 903 (Sept. 12) 1914

<sup>31</sup> Noguchi, *J. Exper. M.* **27** 575, 1918, **16** 191, 1912, **30** 13, 1919

reported the results of forty patients with recurrent fever whom he had treated with sodium cacodylate given intravenously, saying that it did not replace arsphenamin in this disease but was efficacious and without the bad effects sometimes occurring with arsphenamin

Sodium cacodylate is the dimethylarsenate of sodium containing a variable amount of water of crystallization (usually about 30 per cent )  $\text{Na} (\text{CH}_3)_2 \text{AsO}_2$  Roasenda<sup>29</sup> ascribes its low toxicity to the fact

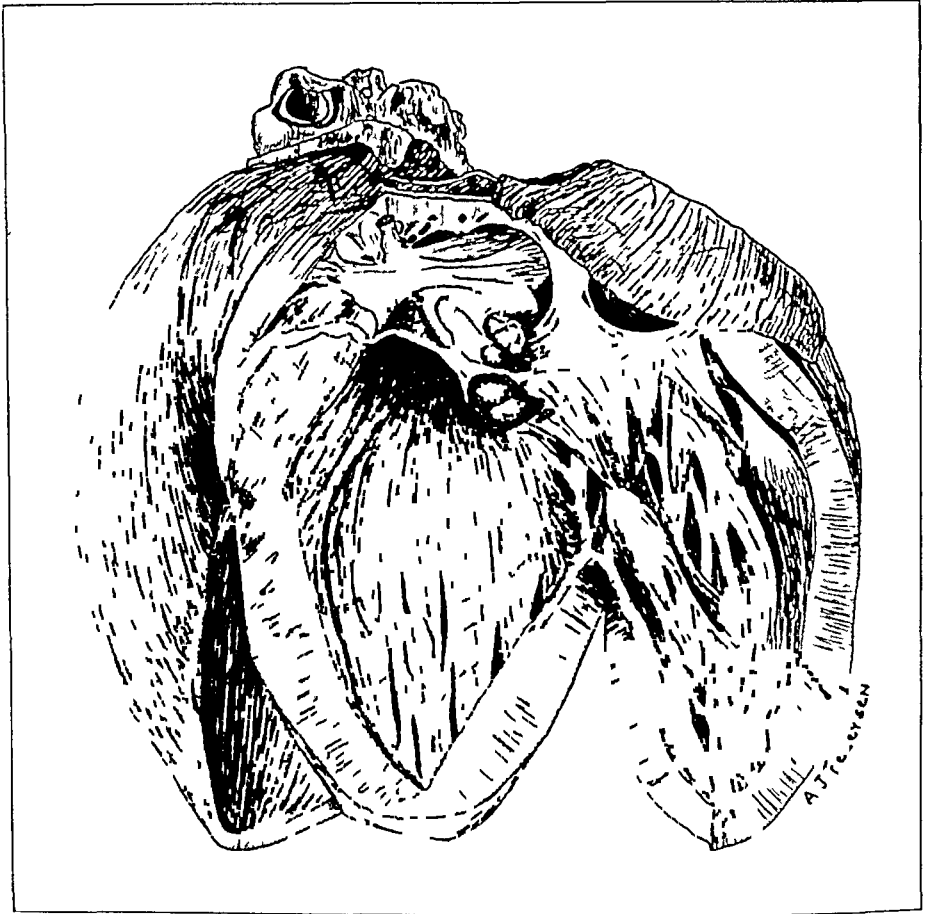


Fig 2—A thrombo-ulcerative mitral endocarditis

that it does not dissociate, and the effects are obtained by partial reduction, decompositions and transformations (probably oxidations) when in contact with tissue fluids

#### ANIMAL EXPERIMENTATION

The observations recorded here concern (1) the production of endocarditis in animals by the injection of strains of *Streptococcus viridans* obtained by blood cultures from patients suffering from chronic

his patients outside of hospitals in whom a subacute or chronic bacterial or infectious endocarditis was diagnosed, a positive blood culture of *Streptococcus viridans* was obtained in thirty-five, an alphahemolytic streptococcus (Brown) in two, a total of thirty-seven, or 84 per cent, during the year.

Rabbits weighing approximately from (1.8 kg to 2.2 kg) 4 to 5 pounds and apparently in good health were selected. Salt solution suspensions of *Streptococcus viridans* cultures, forty-eight hours old, grown on human blood agar slants, were injected into the marginal ear vein and intracardially, and the animals carefully watched, cultures made from their blood at intervals of several weeks under aseptic precautions by introducing a large needle into the ear vein of the rabbit and

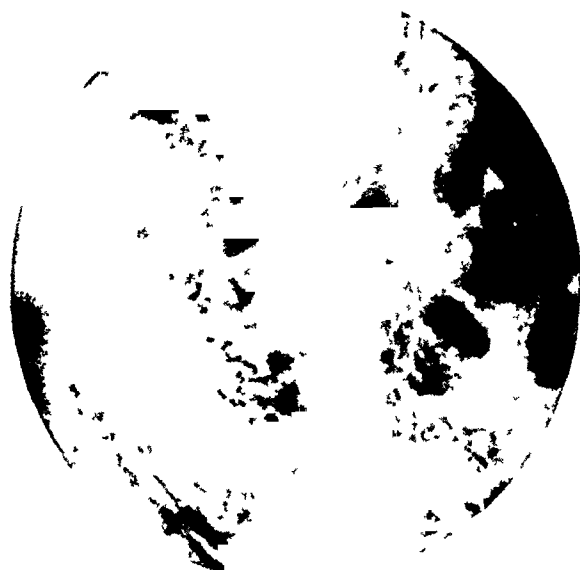


Fig 5—A small portion of the vegetation of Fig 1 demonstrating the bacteria ( $\times 1200$ )

catching the blood drops in Petri dishes. The cultures of the blood were made as described. Leukocyte counts were made at intervals and the general condition of the rabbit observed. (The introduction of the needle into the ear vein is an easy procedure and serves as a much more efficacious means of drawing blood than the usual method of cutting the marginal ear vein of the rabbit with a razor.)

The report of endocarditis produced includes only such as were proved by postmortem examination.

*Results*—Of fifty-three rabbits injected, forty-six have either died or have been killed and an endocarditis or pericarditis or both has been demonstrated in thirty-eight, and of the thirty-eight an endocarditis in thirty-five, or a total of almost 80 per cent. Table 1 illustrates the occurrence of an endocarditis in ten rabbits, serving as controls for

blood, were used at times Detweiler's<sup>32</sup> modification of Rosenow's method in which the centrifuged blood sediment is incubated in bouillon for twenty-four hours and then planted according to the Rosenow method proved satisfactory Blood agar plates were made at the bedside, the layer of blood agar covered by another layer of agar, this by melted paraffin and the plates and bouillon tubes taken immediately to the incubator Holman's<sup>33</sup> serum sugar broth was used in making cultures of the supernatant blood serum, and all the streptococci were



Fig 4—A small vegetation of the endocardium of the mitral valve ( $\times 170$ )

classified according to their sugar-fermentation reactions All mediums were titrated colorimetrically to a  $p_H$  7.6 Approximately 35 c.c. of blood were withdrawn from the median cubital vein of patients

Of forty-four patients of Drs. A. R. Ellhott, R. B. Preble, N. C. Gilbert, J. L. Miller and J. A. Capps at St. Luke's Hospital and several on the service of Dr. Capps at the Cook County Hospital and a few of

<sup>32</sup> Detweiler, H. K., and Robinson, W. L. Experimental Endocarditis  
*J. A. M. A.* **67** 1653 (Dec. 2) 1916

<sup>33</sup> Holman. *J. M. Res.* **34** 377, 1916

In several animals, the injection of cacodylate was begun immediately after the injection of the suspensions of *Streptococcus viridans*

In other animals, a series of cacodylate injections was given, followed by huge or as near as possible lethal doses of *Streptococcus viridans*. An equal number of rabbits received the same size of streptococcus suspensions. Still others received a series of cacodylate injections followed by a smaller suspension of *Streptococcus viridans*, not enough to kill if possible. A corresponding number again received



Fig 7—A healing mitral endocarditis (note the granulation tissue)

the streptococcus suspensions alone. This series had the injection of streptococci repeated three days after the first injection, each time preceding the streptococcus injections by a rather large dose of cacodylate in one-half of the animals.

*Results*—In Table 1 are collected the results of the injection of suspensions of streptococci with the development of an endocarditis. Urine obtained at postmortem contained at times erythrocytes and albumin indicating renal infection and at others casts and albumin alone. The valvular changes illustrated are of an aortic (Fig 1), a

the ten of Table 2 to be discussed later. The animals were weighed approximately every two weeks.

## (2) Arsenical Therapy

These experiments were carried out to determine the effect of sodium cacodylate on the clinical course of an endocarditis in rabbits.

*Methods*—Distilled water solutions of sodium cacodylate (Malinckrodt, U S P) were injected into the marginal ear vein of rabbits in doses of from one-half a grain to 3 grains a day, for periods vary-



Fig 6—An extensive aortic endocarditis

ing from two weeks to ten weeks. It is generally believed among clinicians that the peculiar odor of the patients' excreta, an odor resembling garlic, is evidence of the potency of the sodium cacodylate. This odor was used as a criterion for increasing the dose of the drug in the rabbits. Cultures of the blood were made approximately every two weeks. The rabbits listed in Table 2 were carefully observed for clinical endocarditis or its complications. In a small percentage of the animals an arthritis of the feet developed. When an endocarditis was demonstrated by positive blood culture the injections of sodium cacodylate were begun.

TABLE 2—*Illustrating the Results Obtained with Ten Rabbits Receiving Sodium Cacodylate Intravenously*

Rabbit	Weight in Pounds at Intervals	Date of Injection of Streptococci	Amount Injected, Saline Suspensions	Blood Culture Positive	Leukocyte Counts at Intervals	Cacodylate First Dose	Total Cacodylate of Sodium	Date and Manner of Death	Urine at Necropsy	Postmortem Findings	Remarks
101	9/23/22, 4 10/23/22, 3.62	9/23/22	The washings of 3 blood agar slants	1	7,600, 9/23/22, 6,100, 10/4/22	½ grain 10/8/22	16 grains in 6 weeks	11/12/22, killed with ether	Bladder empty	Recent tricuspid and mitral thrombo-ulcerative endocarditis, fibrous mitral endocarditis, fresh infarct of the right lung thrombo-ulcerative mitral endocarditis, healed fibrous tricuspid and mitral endocarditis, multiple subpleural hemorrhages	Strong "garlic odor" Oct 18, arthritis of the front feet, marked anemia, noted during disease In the recent valve lesion, there were many cocci "garlic odor" is above
102	9/21/22 to 12/20/22, 4.94, 4.7, 5.12	9/21/22	The washings of 3 blood agar slants	2	8,000, 9/21/22, 9,900 9/25/22, 7,800, 10/4/22	½ grain 10/6/22	16 grains in 6 weeks	12/20/22, killed with ether	Bladder empty	Recent thrombo-ulcerative mitral endocarditis, healed fibrous tricuspid and mitral endocarditis, multiple subpleural hemorrhages	In the recent valve lesion, there were many cocci "garlic odor" is above
103	12/29/22, 3.62, Jan 1923, 3.75, 3.75, 3.16	12/29/22	The washings of 3 blood agar slants	3	11,500, 1/18/23	½ grain 1/11/23	11 grains in 2 weeks	1/23/23, died	Trace of albumin, erythrocytes	Slight serofibrinous and fibrous pericarditis, slight fresh tricuspid endocarditis, healed mitral endocarditis, slight ascites	The blood culture at postmortem grew many gram positive green producing cocci probably reinfection
104	12/29/22, 6.16, Jan 1923, 6.25, 5.87, 6 Jan, 1923	12/29/22 and 1/10/23	(1) The washings of 3 blood agar slants (2) of 2 blood agar slants	2	10,800, 1/18/23	½ grain 1/10/23	15 grains in 2 weeks	1/24/23, killed with ether	Albumin, few erythrocytes	Huge fibrinopurulent pericarditis (Cor villosum), and slight fibrous pericarditis, compression atelectasis of the lungs	The pericardial sac filled nine tenths of the chest cavity "garlic odor" of its content was strong
105	12/29/22, 5.62, Jan 1923, 5.62, 5.87, 5.62, 6.16	12/29/22	The washings of 3 blood agar slants	1	8,600, 1/18/23, 11,400,	½ grain 1/8/23	14 grains in 2 weeks	1/31/23 killed with ether	Albumin, few erythrocytes	Healed fibrous and fibrinous pericarditis, multiple subepicardial hemorrhages, hyperplasia of the spleen	Very large spleen the animal seemed entirely well when killed
106	12/29/22, 3.87, Jan and Feb, 4.37, 4.44, 4.62, 5.62	12/29/22	The washings of 3 blood agar slants	3	9,500, 1/18/23, 9,200, 1/29/23	½ grain 1/8/23	18 grains in 3 weeks	2/6/23 killed with ether	Bladder empty	Healed fibrous aortic endocarditis, marked obliterative fibrous pericarditis	No bacteria grew in a blood culture at postmortem
107	10/12/22, 5.5 10/23/22, 5.4 12/6/22, 6.5 1/11/23, 5.4 2/7/23, 6.37	10/12/22	The washings of 3 blood agar slants	2	9,600 1/29/23	½ grain 1/13/23	40 grains in 4 series of 2 weeks each	2/7/23 killed with ether	Clear urine, no albumin or red cells	Healed fibrous and localized fibrinous pericarditis, healed right mural endocarditis, hypostatic hyperemia of the lungs	Animal sick in October, apparently better in November and sick in January, and became well the last 2 weeks of January
108	2/20/23, 6.5 3/6/23, 6.75 3/19/23, 7 4/2/23, 4.5	2/24/23	The washings of 6 blood agar slants	1 (neg culture it necropsy)	8,800 2/22/23	1 grain 2/27/23	31 grains in 2 weeks	4/2/23, died	Scanty Many hyaline casts albumin	Recent thrombo-ulcerative tricuspid endocarditis, complete infarction of the lower lobe of the right lung, acute nephritis	Moderate salivatic on the last day of the cacodylate in jection
109	2/20/23, 5.2 3/6/23, 4.75 3/14/23, 4	2/24/23	The washings of 6 blood agar slants	1	14,000 2/22/23	1 grain 2/27/23	14 grains in 2 weeks	3/14/23, died	Bladder empty	Fresh thrombo-ulcerative mural endocarditis of both auricles, healing pericarditis, bronchopneumonia	March 7, animal became more listless and March 11 began to froth and have diarrhea
110	2/20/23, 6.4 3/6/23, 7 3/19/23, 7.2 4/3/23, 6.2	2/24/23	The washings of 6 blood agar slants	2	9,000, 2/22/23	1 grain 2/27/23	29 grains in 2 weeks	4/3/23 died	Albumin, granular casts, erythrocytes	Mural thrombo-ulcerative tricuspid endocarditis, embolic (?) lobar pneumonia, R U L and R M L, healed fibrous pericarditis	Up to the last week the animal seemed to be doing well, pneumonia apparently killed him



TABLE 1—*Illustrating the Development of Endocarditis in Ten Rabbits*

Rabbit	Weight in Pounds	Strain of Streptococcus	Date of Injection	Amount Injected, Normal Saline Suspensions	Blood Cultures	Date of Death	Postmortem Findings	Remarks
10	9/11/22, 4 10/ 2/22, 3.7	B <sub>1</sub>	9/11/22	The washings of 2 blood agar slants	5 positive during life, many colonies at necropsy	10/ 2/22	Extensive thrombo ulcerative endocarditis, generalized fibrinopurulent pericarditis	Severe arthritis of the right front foot 4 days after injection, progressive emaciation
11	10/12/22, 4.2 10/25/22, 3.9 12/ 6/22, 5.37 12/26/22, 3.5 12/29/22, 3.87 1/ 8/23, 3.5	W <sub>1</sub>	10/12/22	The washings of 3 blood agar slants	1 negative 10/12/22, 1 positive 11/12/22, necropsy positive	12/26/22	Vegetative aortic and tricuspid endocarditis, multiple subcapsular renal hemorrhages	Severe chill shortly after the first injection
12	12/29/22, 3.87 1/ 8/23, 3.5	S <sub>2</sub>	12/29/22	The washings of 2 blood agar slants	150 colonies on one plate, 12/30/22, many colonies at death	1/ 8/23	Fresh thrombo ulcerative mitral endocarditis (mitral stenosis), fresh infarcts of the kidneys, marked hyperplasia of the spleen	Severe chill at the time of injection, a rapid, septic course
13	12/29/22, 5.75 1/22/23, 5.5 3/16/23, 5.7 3/19/23, 5 2/20/23, 4 3/17/23, 2.62	W <sub>3</sub>	12/29/22	The washings of 4 blood agar slants	2 positive and 1 negative during life, many colonies at necropsy	4/19/23	Fresh thrombo ulcerative tricuspid and mitral endocarditis, embolic abscesses of the right lung, healed fibrosis pericarditis	Urine, large amount of albumin, Streptococcus viridans recovered from lung abscesses
14	2/20/23, 4 3/17/23, 2.62	W <sub>7</sub>	2/24/23	The washings of 6 blood agar slants	1 positive during life, many colonies at necropsy	3/17/23	Huge mural thrombo ulcerative endocarditis of the right auricle and the tricuspid valve, passive hyperemia of the lungs	Urine, a few erythrocytes and a trace of albumin, progressive, rapid emaciation after the first week
15	2/20/23, 5.37 3/ 2/23, 5	N <sub>2</sub>	2/24/23	The washings of 5 blood agar slants	1 positive during life, many colonies at necropsy	3/ 2/23	Acute vegetative mitral endocarditis, multiple subpleural and renal subcapsular hemorrhages, acute hyperplasia of the spleen	Urine, a moderate amount of albumin, few erythrocytes
16	3/27/23, 5.44 4/30/23, 4.37	N <sub>2</sub>	3/28/23	The washings of 8 blood agar slants	Many colonies at necropsy	4/30/23	Healing thrombo ulcerative tricuspid endocarditis, multiple subpleural hemorrhages	Urine, very many epithelial cells
17	3/20/23, 5 3/26/23, 5.5	W <sub>3</sub>	3/26/23	The washings of 8 blood agar slants	Many colonies at necropsy	3/28/23	Acute thrombo ulcerative mitral endocarditis, multiple renal infarcts, embolic lobar pneumonia (R L L)	Rapid septic course of 2 days urine, trace of albumin, few erythrocytes, many renal epithelial cells
18	3/10/23, 4.37 3/30/23, 3.75 5/ 3/23, 3	N <sub>2</sub>	3/10/23	The washings of 6 blood agar slants	1 positive during life, positive at necropsy	5/ 3/23	Fresh mural thrombo ulcerative endocarditis of the right auricle, moderate ascites	April 1, arthritis of the left front foot, listlessness, loss of weight, urine, small amount of albumin and erythrocytes
19	3/10/23, 4.75 3/30/23, 4.25 3/ 3/23, 3.25	C <sub>1</sub>	3/10/23	The washings of 6 blood agar slants	1 positive during life, positive at necropsy	5/ 3/23	Slight acute vegetative aortic endocarditis	Arthritis of the right front foot shortly before death, urine, trace of albumin

TABLE 3—Results of Injection of Sodium Cacodylate Followed by Huge Doses of Normal Saline Suspensions of *Streptococcus Viridans*—  
42, 44, 49 and 51 Being Controls

Rabbit	Weight in Pounds	Sodium Cacodylate Injected	Strain of Streptococcus	Amount of Saline Suspension Injected	Length of Life After Injection	Postmortem Findings
41	5.5	17 grains, 2 grains first day, then 3 gr daily for 5 days	M <sub>3</sub>	The washings of 8 blood agar slants	65 days	Slight mural endocarditis of the left auricle and right ventricle (partial calcification), healing renal infarcts
42	5.62	None	M <sub>3</sub>	The washings of 8 blood agar slants	8 days	Extensive thrombo ulcerative aortic endocarditis, multiple renal infarcts, huge hyperplasia of spleen
43	6	6 grains, 3 grains daily for 2 days	W <sub>3</sub>	The washings of 10 blood agar slants	30 hours	Fibrinopurulent pericarditis, bronchopneumonia, bilateral pleuritis
44	4.75	None	W <sub>3</sub>	The washings of 10 blood agar slants	20 hours	Mural thrombo ulcerative right and left endocarditis, multiple subcapsular renal hemorrhages
48	6	6 grains, 3 grains daily for 2 qlys	M <sub>3</sub>	The washings of 10 blood agar slants	11 days	Huge thrombo ulcerative (verrucous) aortic endocarditis, multiple renal infarcts
49	5.25	None	M <sub>3</sub>	The washings of 10 blood agar slants	4 days	Thrombo ulcerative mitral (vegetative) endocarditis, slight ascites, marked passive hyperemia of the liver
50	5.75	6 grains, 3 grains daily for 2 days	B <sub>2</sub>	The washings of 10 blood agar slants	72 hours	Multiple subendocardial hemorrhages of the right auricle, renal infarcts, fibrinous pericarditis
51	5.37	None	B <sub>2</sub>	The washings of 10 blood agar slants	Less than 20 hours	Thrombo ulcerative (vegetative) mitral and tricuspid endocarditis, complete infarct of one lung lobe

TABLE 4—Results Obtained with Two Rabbits Given Cacodylate Immediately After Injecting *Streptococci* and for Weeks Thereafter

Rabbit	Weight in Pounds at Intervals	Strain of Streptococcus	Amount of Streptococcus Injected and Date	Blood Culture	Sodium Cacodylate (1) Initial Dose (2) Total (3) Time	Date Killed	Postmortem Findings
111	4.3, 4.1, October	W <sub>4</sub>	Washings of 3 blood agar slants 10/12/22	Two cultures negative 2 weeks apart	(1) ½ grain 10/13/22 (2) 15.25 grains (3) 5 weeks	11/18/22	No changes of any of the organs
112	4.3, 4.1, 10/12/22, 5.7, 5.6, 2/20/23	S <sub>1</sub>	Same as 111	Culture negative 10/18 and 11/2/22, 1/17 and 1/20/23 (4)	(1) ½ grain 10/13/22 (2) 45 grains (3) Oct 13 to Jan 31 with intervals of rest	2/20/23	Small fibrous tag of the pericardium, healed renal infarcts

mitral, (Fig 2) and a tricuspid (Fig 3) endocarditis, of which there were many demonstrated

The extent of the endocarditis varied, with some animals there was almost a complete stenosis of the valve, while others had only a few vegetations. Gross lesions were examined microscopically, except a few in which section would have destroyed a tissue otherwise valuable for gross demonstration. The tissues were stained for bacteria by the Goodpasture<sup>34</sup> method, and in many of the endocardial vegetations diplococci and cocci in short chains were demonstrated



Fig 8—A further organized clot of the tricuspid valve ( $\times 60$ )

In Table 2 are collected the results of the injection of ten rabbits with sodium cacodylate after an endocarditis had been demonstrated by blood culture. Six were killed with ether one to two months after their injection with streptococci, at which time they had apparently recovered from the infection. Four died. The postmortem changes were those of an endocarditis, active, healing or healed, or a pericarditis. The figures in the "Blood Culture" column indicate the number of times a positive culture was obtained during life.

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34 Goodpasture Medical War Manual, No 6, 1919, p 349

TABLE 5—The Results of Repeated Injections of *Streptococcus Viridans* Preceded by Injections of Sodium Cacodylate, 53, 55, 57, 59 and 61 Serving as Controls

Rabbit	Weight in Pounds at Intervals	Amount of Sodium Cacodylate and the Date of Injection	Amount of Saline Suspension of <i>Streptococcus Viridans</i>	Sodium Cacodylate Repeated <i>Streptococcus</i> Injection Repeated	Length of Life After First Injection	Postmortem Findings
52	May 19, 3.3 May 24, 3.3 May 29, 3.2 June 8, 2.75	May 19, 3 grains May 20, 3 grains May 21, 3 grains	The washings of 3 blood agar slants several seconds after the cacodylate, May 21, 1923	May 24, 2 grains followed by the washings of 1 blood agar slant, May 24	Alive and in good condition 20 days	
53	May 19, 4.5 May 24, 4.7 May 29, 3.7 June 4, 3.3	None	The washings of 3 blood agar slants, May 21, 1923	The washings of 1 blood agar slant, May 24	Died, June 4, 1923	Multiple subpericardial and pulmonary abscesses, slight serofibrinous pericarditis, acute hyperplasia of the spleen
54	May 19, 4 May 24, 3.8 May 29, 3.3 June 8, 2.8	May 19, 3 grains May 20, 3 grains May 21, 3 grains	The washings of 3 blood agar slants several seconds after the cacodylate, May 21, 1923	May 24, 2 grains followed by the washings of 1 blood agar slant	Alive and in good condition 20 days	
55	May 19, 4 May 24, 3.75	None	The washings of 3 blood agar slants, May 21, 1923	The washings of 1 blood agar slant, May 24	Died, May 25, 1923	Slight, fresh thrombo ulcerative mitral endocarditis, slight fibrinous pericarditis
56	May 19, 3.02	May 19, 3 grains May 20, 3 grains May 21, 3 grains	The washings of 3 blood agar slants several seconds after the cacodylate, May 21, 1923		Died, May 23, 1923	Bilateral hemothorax, marked edema and hyperemia of the lungs, slight fresh thrombo ulcerative endocarditis
57	May 19, 3.5 May 24, 3.5	None	The washings of 3 blood agar slants, May 21, 1923	The washings of 1 blood agar slant, May 24	Died, May 28, 1923	Extensive thrombo ulcerative tricuspid endocarditis, serofibrinous pericarditis and bilateral pleuritis
58	May 19, 3.3 May 24, 2.8 May 29, 2.2 May 31, 1.9	May 19, 3 grains May 20, 3 grains May 21, 3 grains	The washings of 3 blood agar slants several seconds after the cacodylate, May 21, 1923	May 24, 2 grains followed by the washings of 1 blood agar slant	Died, May 31, 1923	Recent thrombo ulcerative mitral and mural endocarditis, multiple healing infarcts of the kidneys, fibrinous pleuritis
59	May 19, 3.3 May 24, 2.8	None	The washings of 3 blood agar slants, May 21, 1923	The washings of 1 blood agar slant, May 24	Died, May 26, 1923	Extensive thrombo ulcerative (verrucous) tricuspid endocarditis
60	May 19, 3.5 May 24, 3.2 May 29, 2.8 June 8, 2	May 19, 3 grains May 20, 3 grains May 21, 3 grains	The washings of 3 blood agar slants several seconds after the cacodylate, May 21, 1923	May 24, 2 grains followed by the washings of 1 blood agar slant	Died, June 8, 1923	No evidence of endocardial infection, the only gross finding, marked emaciation
61	May 19, 4.3 May 24, 4.2 May 29, 3.6 June 8, 2.8	None	The washings of 3 blood agar slants, May 21, 1923	The washings of 1 blood agar slant, May 24	Died, June 9, 1923	Thrombo ulcerative tricuspid and mural endocarditis, healing lung infarcts, fresh splenic infarct

The photomicrographs illustrate various stages of the endocarditis, from a small endocardial vegetation to an extensive thrombo-ulcerative endocarditis (4, 5 and 6), and from a healing mitral to a healed fibrous endocarditis (Figs 7, 8 and 9)

In Table 4, two rabbits illustrate results with the injection of suspensions of *Streptococcus viridans* followed the day after by an injection of a small dose of cacodylate, and for several months thereafter. At necropsy, in one, two, in the other, four months after the injection of the streptococcus, when they seemed well, no heart changes were noted, but in the latter several scars of renal infarcts were demonstrated



Fig 9—A completely healed fibrous mitral endocarditis ( $\times 135$ )

When the rabbits were injected with rather large doses of cacodylate followed by huge suspensions of *Streptococcus viridans*, the results represented by Table 3 are noteworthy in that in each case the animal receiving the cacodylate before the streptococcus lived longer than the control which received no cacodylate. Rabbit 41, receiving the longest course, died seventy days after injection with the streptococcus, while the control rabbit died eight days after injection. In the other six, the difference was not as marked, yet distinct.

that they perhaps stimulate the endothelial cells of blood vessels and blood sinuses to greater phagocytosis

#### CONCLUSIONS

1 In 84 per cent of a group of patients in whom a chronic infectious endocarditis was suspected *Streptococcus viridans* was recovered by blood culture

2 The essential needs for the isolation of *Streptococcus viridans* from the blood of patients during life seem to be anaerobic conditions, mediums rich in nutrient substances (liquid or solid), careful daily examinations of all mediums used for at least a week, and the withdrawal of a large quantity of blood (from 30 to 40 c c ) at the proper time

3 Sodium cacodylate seems to have some beneficial influence on the healing of heart valve infections

4 Arsenical preparations, such as sodium cacodylate, may have a protective power for the endocardium or the pericardium

The ten rabbits of Table 5 illustrate results similar to those of Table 3, but here a smaller suspension of streptococci was injected and another small suspension injected three days later, in five a course of cacodylate being given for several days and a single injection of cacodylate immediately before each injection of streptococci and in the other five only the streptococci. Four of the controls died soon, one of the animals receiving the cacodylate died five days after the control, receiving no cacodylate, and the other died two days after its initial injection from an extensive hemothorax and a slight tricuspid endocarditis. The other two rabbits receiving the cacodylate are still living and appear well. The fifth control died twenty days after injection with the streptococci.

Of the other animals not mentioned in the tables, some died of an endocarditis or a pericarditis later. One developed a marked cystitis and pyelitis and died of pneumonia later. Others died of bites inflicted by their mates. One control animal seemed well and when killed four months later some ascites and a healed splenic infarct were demonstrable. Five of the fifty-three rabbits are still living.

The term thrombo-ulcerative is the generally recognized designation by pathologists of the endocardial lesions of chronic infectious endocarditis.

#### DISCUSSION

This report suggests possibilities for the specific therapy of valvular endocarditis. While the results obtained with forty-eight rabbits do not establish conclusively the value of sodium cacodylate therapy with chronic infectious endocarditis, yet they afford reasons for believing that it is of some value.

The "selective actions" or "elective activity" of *Streptococcus viridans* isolated from patients with endocardial lesions for the endocardium and pericardium of rabbits has been repeatedly demonstrated by Rosenow and others. The fact that 80 per cent of rabbits injected developed such an endocarditis in this series seems to stress the "selective action" of this coccus. At times the endocarditis develops with remarkable rapidity, the shortest time noted being twenty hours. The rapidity of production of an endocarditis may be influenced by the virulence of the streptococci, the amount of the suspension injected, the weight of the animal, and its general condition and other factors not recognized at this time.

Animals receiving repeated injections of cacodylate first and then huge suspensions of streptococci seem to be better able to destroy the streptococci than those receiving no previous sodium cacodylate injections. It has been suggested by immunologists that such preparations as sodium cacodylate may have a protective influence for the host in

in the continental literature (Israel,<sup>1</sup> Rodet,<sup>2</sup> Lexer,<sup>3</sup> Jordan,<sup>4</sup> Schmitz,<sup>5</sup> Barth<sup>6</sup>) More recently American observers have published clinical and experimental data which in no way refute, but augment such observations (Brewer,<sup>7</sup> Richardson,<sup>8</sup> McKenzie,<sup>9</sup> Phemister<sup>10</sup> and others)

For the past few years I have attempted to establish the portal of entry in cases of primary perirenal abscess, that is, abscesses which are not caused by continuity from adjoining diseased tissues Cortical renal abscesses are the exception, however, and are not included, as the perirenal tissue is often involved by the outward extension of minute cortical collections of pus The incidence of boils and carbuncles preceding such perirenal abscesses is high, and cultural methods yield *Staphylococcus aureus* from the evacuated pus in the majority of these cases Similarly I have been interested in cases of muscle abscess, acute osteomyelitis and suppurative nephritis and their etiologic relationship to foci on the skin

Recently, Phemister,<sup>10</sup> under the title of hematogenous staphylococcus infections secondary to foci in the skin, has grouped a series of cases similar to those reported below He has reviewed the clinical and experimental literature from an authentic bibliography, and his cases exemplify his title clearly I report these additional cases because it is felt such data will impress more thoroughly the etiologic and clinical facts so correctly intimated by his paper

These cases are reviewed, with but four exceptions, from the records of the University of California Medical School Two cases are taken from my notes during the recent war

#### ACUTE UNILATERAL SUPPURATIVE NEPHRITIS

There is a difference of opinion as to which organism most frequently causes cortical abscess Israel finds *B. coli* most frequent, but staphylococcus is a more common etiologic agent than the streptococcus, pneumococcus or the typhoid bacillus There is some question as to whether the colon bacillus is a primary or secondary invader in many cases

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1 Israel Chir Klin d Nierenkrankheiten, Berlin, 1901, p 580

2 Rodet Rev de Chir **5** 272, 1885

3 Lexer Arch f klin Chir **53** 266, 1896

4 Jordan Chir Congress, 1905, p 18

5 Schmitz Centralbl f Bakteriöl **65** 259, 1912

6 Barth Arch f klin Chir **114** 477, 1920

7 Brewer Surg, Gynec & Obst **2** 485, 1906

8 Richardson Surg, Gynec & Obst **21** 1, 1915

9 McKenzie Canadian M A J **11** 714, 1921

10 Phemister Hematogenous Staphylococcus Infections Secondary to Foci in the Skin, J A M A **78** 480 (Feb 18) 1922



# THE COMPLICATIONS OF STAPHYLOCOCCUS FOCAL INFECTIONS \*

LAIRD M MORRIS, M D

SAN FRANCISCO

Ordinarily staphylococcic septicemias present a fulminating septic picture classically represented by repeated chills, fever, delirium, purpura, endocardial murmurs and multiple abscesses. The blood picture shows a leukocytosis and an anemia. Cocci are easily grown from the blood by the ordinary cultural methods. The infectious focus may be a minute pyogenic skin infection, a furuncle, a discharging ear or a suppurating sinus. Of these foci, the most important are the sources from the skin. Such a pyemic state is represented by generalized multiple abscesses of the organs, more particularly minute suppurative foci in the kidneys, heart muscle and lungs. Commonly the mitral and aortic valves show large thrombus masses with rapid destruction of the leaflets. The muscles, the medullary cavities of the long bones or joints may show collections of yellowish pus, from which cocci are readily grown. A pyemia which represents the acute type described can be experimentally simulated in rabbits by comparatively large intravenous injections of *Staphylococcus aureus*.

I do not care to emphasize this type, but that group of staphylococcus cases which is best represented by metastatic abscesses, commonly single, occasionally multiple, in various anatomic structures of the body. This group is representative of an intermittent blood stream infection from some focal origin, usually from boils, carbuncles, paronychia, impetigo or infected skin wounds. So striking is a history of a staphylococcus skin infection, succeeded at an unstated short interval of time by a clinical picture of perinephric abscess, unilateral suppurative nephritis or an acute osteomyelitis, and so constant are the cultural findings in the distant lesions compared with the primary focus, that the relationship of a focal skin infection to a metastatic internal lesion is given clinical proof.

Experimental, pathologic and clinical data regarding these focal skin associations with fairly constant metastatic lesions was first mentioned

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\* From the medical department of the University of California Medical School

\* The reviewed cases were seen in the medical and pediatric services of the University Hospital and San Francisco Hospital. Drs Moffitt, Lucas, Ebricht, Kerr

Operative procedures were performed in the surgical services of these hospitals, Drs Brunn, Pope, Hinman, Baldwin

red blood cells, pus casts and a positive culture from the ureter of the diseased side. Occasionally urinary findings are negative, and Richardson's<sup>8</sup> third conclusion is timely in this respect. "A urine normal on clinical examination does not exclude the possibility of cortical renal abscess." Ordinarily a delayed "appearance time" of phenolsulphonephthalein from the diseased kidney and a marked diminution in the quantity of the dye eliminated are fairly constant findings. Bait<sup>6</sup> believes the functional test is the best single urinary test.

#### TYPE CASES OF ACUTE SUPPURATIVE INFLAMMATION OF THE KIDNEY

CASE 1—J. R. C., a man, aged 57, in December, 1915, began to feel a little below normal, and a "sore" appeared on the left side of the nose, from which considerable pus was discharged. He was confined to bed toward the end of the month because of fever, pain in the limbs and general malaise. Stiffness and tenderness increased in the thigh muscles. He entered the hospital about the middle of February. Physical examination revealed lungs, clear, heart, normal, spleen slightly enlarged and palpable, tender and palpable left kidney, with pain in the left kidney region radiating toward the back. The temperature was 38 C (100.4 F) and the white cell count was 9,800. The Wassermann test was negative. Catheterized urine contained *Staphylococcus aureus*. A specimen from the left ureter contained pus. Cystoscopy revealed diffuse granular cystitis. The results of the intravenous phenolsulphonephthalein test for renal function were: left ureter, appearance time, 8 minutes, fifteen minutes, 45 per cent, thirty minutes, 3 per cent, total, 75 per cent; right ureter, appearance time, 5 minutes, fifteen minutes, 7 per cent, thirty minutes, 10 per cent, total, 17 per cent.

Feb. 18, 1916, the left kidney was removed. Gross Pathology. There were yellowish necrotic areas of pinhead size at the upper pole and a large solitary abscess at the lower pole. On section the pelvis seemed rather small and the wall thick and edematous. Culture from the pus contained *Staphylococcus aureus*.

The patient was discharged well.

CASE 2—L. S., a man, aged 34, had been in a run-down condition since he had had influenza two years before. He had a slight cough. Two months before entering the hospital, he complained of a boil on his left foot and another on the right jaw. About a month ago, he began to have acute pain in the right lumbar region. Shortly after this he noticed pus in the urine. The pain radiated through to the right midabdomen. The patient complained of sweats, weakness and loss of weight. Physical examination revealed no active tuberculosis. There were signs of thickened pleura or high diaphragm on the right with limitation of motion. The liver and spleen were not palpable. There was marked tenderness over the lumbar region on the right. The temperature was 38.5 C (101.7 F). The white blood cells numbered 16,200. Cystoscopy. Cultures from bladder contained *Staphylococcus aureus*. Urine from the left kidney was sterile. According to the history, the right kidney did not function and contained no urine at this time, but a guinea-pig was apparently inoculated with a specimen from the right kidney according to a later note.

August 16. Operation. A perirenal abscess was drained, and nephrectomy was performed. There was pus in the perinephric fat, and there was a cortical abscess at the lower pole of the right kidney.

Gross Pathology. At the lower anterior pole there was a slightly projecting capsular abscess about 2 cm in diameter. On section, proceeding from

The condition may follow abscess formation in the skin at varying intervals of time. It is characteristic of micro-organisms in general, having gained entrance in the blood stream, to be excreted by the kidneys when not disposed of by the natural defenses of the host. The peculiarity of staphylococcus is that it grows ordinarily in clumps and clings together rather than spreads diffusely. These small groups lodge primarily in the glomeruli, and their pathogenicity calls forth abscess formation in the peripheral substance of the kidney proper, subcapsular abscesses. Thus the name of kidney carbuncle has been given to such conditions by Israel. These lesions of the kidney are almost invariably multiple, their multiplicity and size depending primarily on the number of organisms deposited at various time intervals. Such minute abscesses often become confluent. This pathology is in marked distinction to that produced by *B. coli* which, because of low pathogenicity, may pass through the kidney leaving little or no trace of their course except cloudy swelling of the tubules in their convoluted portion, producing an inflammatory reaction in the pelvis proper. Pyelonephritis, and the more advanced condition pyelonephrosis, most commonly caused by *B. coli*, is best considered an ascending infection from the pelvis to the kidney substance proper. This condition shows a different pathologic picture from the conglomerate cortical abscesses above described, although cortical abscesses are common in this condition. The acute diffuse inflammation of the kidney which is caused by blood-borne *B. coli* infection seldom shows abscess formation (Ward<sup>11</sup>). Renal cortical suppurations of staphylococcus origin are dissimilar to lesions caused by *Streptococcus viridans*, for, while localizing primarily in the glomeruli, they cause no pus formation but terminally a chronic glomerulonephritis (Baehr<sup>12</sup>). Larger emboli characteristically cause septic infarcts in the renal cortex, which may break down, forming abscesses similar to those of staphylococcus. *Streptococcus hemolyticus* causes abscesses more commonly than *Streptococcus viridans*, however. Renal tuberculosis, either of the caseocavernous type or that form showing multiple tuberculosis foci in the cortex with or without perinephritis, is of a far more chronic nature.

Of importance in cases of acute unilateral hematogenous suppurative nephritis of the kidney is a diminished resistance of one kidney as a result of previous disease or injury (Israel,<sup>1</sup> Brewer,<sup>7</sup> and others). The clinical picture is usually that of mild toxemia, although at times acutely stormy (Brewer,<sup>7</sup> Ward<sup>11</sup>). Localized pain and tenderness in the hypochondrium and costovertebral region are signs of importance. Abnormal urinary findings complete the picture, that is, pus cells,

11 Ward Surg, Gynec & Obst **21** 406, 1915

12 Baehr J Exper M **15** 330, 1912

The patient entered the University of California Hospital three months after her primary trouble. Physical examination revealed a blowing systolic murmur over the base of the heart, extreme rigidity and tenderness in the right hypochondrium and lumbar muscles, slight swelling, mottling and congestion over the lumbar region. The liver and spleen were not enlarged. The Wassermann test was negative. A blood culture was negative. The urine was normal. White blood cells numbered 26,600. There were 93 per cent of polymorphonuclear cells. The roentgen ray showed obliteration of the kidney and a psoas outline on the right. Operation revealed an abscess around the lower pole of the right kidney. The kidney was removed, but no gross pathologic condition was found. Cultures from the pus contained *Staphylococcus aureus*.

CASE 4—W H K, a man, aged 43, entered the hospital on Feb 13, 1916. Five months before he had had an infection of the right hand, with a hard core. This condition cleared up, and he then began to be troubled with pain on the anterior surface of the left thigh. The pain migrated to the ankle joint, which became swollen, but the swelling subsided in a week. While being treated for the condition in the leg, he noted a dull aching pain starting low down in the right side of the abdomen and radiating up to the kidney region. This pain localized in the right upper quadrant and the right lumbar region was "sore." The patient felt weak, his appetite was poor and he had lost weight. He had no chills or sweats.

Examination revealed a sick looking, anemic man, with eyes sunken and yellowish sclerae. The heart was normal. Dulness at the right base seemed to be due more to a high diaphragm than to a pleural collection. Breath sounds still were heard over this area. There was no friction sound. It was impossible to palpate the upper right side of the abdomen on account of rigid abdominal muscles. There was decided tenderness over the right costovertebral angle. The temperature was 100.4 F (38 C). White blood count, 20,000. Catheterized urine from the right kidney did not contain pus, the culture was negative. The phenolsulphonephthalein "appearance time" was 6 minutes (intravenous), in fifteen minutes it was 23 per cent, in the following fifteen minutes 11 per cent. The roentgenogram showed an area of rarefaction in the shaft of the femur 2 inches (5.08 cm) below the trochanter with periosteal reaction over it. The condition was diagnosed as osteomyelitis. Screen examination of the chest showed a high and somewhat flattened right diaphragm. Operation. Pus was drained from the superior and posterior parts of the fatty capsule of the right kidney. The kidney seemed intact and was not removed. Culture from the pus was *Staphylococcus aureus*.

CASE 5—A S, a man, aged 49, entered the hospital with a carbuncle on the neck of three weeks' duration. His present illness started a week ago with pain in the left side of the chest on coughing and deep inspiration. He complained of loss of appetite, weakness and night sweats. Physical examination revealed a normal heart, diminished scarcely audible breath sounds over the left base, with corresponding dulness and diminished vocal fremitus, and no râles. Respirations were short, and attempted deep breathing caused pain low in the left side. The left lumbar region was more prominent than the right, extremely tender and slightly edematous. The temperature was 102 F. White blood count, 29,000. The urine was normal. The chest was tapped, but was dry. Operation. Two hundred and fifty cubic centimeters of pus were removed from the perirenal region, the kidney was not removed. Pus culture contained *Staphylococcus aureus*. There was a marked drop in temperature following operation, and the patient was discharged in three weeks, well.

CASE 6—L J, a man, aged 24, three months before began having a series of boils. These extended over a period of two months. The last boil was on the right forearm and was quite severe. During this interval of time, the patient was treated for an abscess in the palm. About a month later

the abscess toward the pelvis, multiple small focal abscesses were seen. The remainder of the kidney appeared to be quite normal. The pelvis was not dilated or thickened. Culture from pus contained *Staphylococcus aureus*.

The patient was discharged well.

#### DISCUSSION

There is little to be said regarding these fairly typical cases except to point out a preceding skin infection of a staphylococcus nature, and later isolation of cocci of the aureus group from the metastatic lesions. In Case 2 the perinephric fat was involved in contradistinction to Case 1. Such a combined renal-perirenal suppuration must always be borne in mind when simple drainage of the abscessed fatty tissue fails to clear the symptoms.

#### PERINEPHRIC ABSCESS

These abscesses are located in the perirenal fat, and in a pure state they are wholly outside the kidney. Under the caption "primary perinephric abscess" I exclude all perinephritic collections of pus spread by continuity from adjacent diseased sources, except the kidney cortex. This classification excludes perinephritis accompanying pyonephrosis, nephrolithiasis and renal tuberculosis. In the majority of primary cases there is an extension of a minute cortical abscess, probably seldom the reverse. It is stated, however, that a pure perirenal abscess may be the only internal lesion from some cutaneous infection. Such cases may show no abnormal urinary findings and clear readily by simple drainage of the part in many instances.

The picture caused by these extraneuphric collections of pus is more severe than that caused by a suppurative kidney proper. The toxemia may be more marked, probably because of rapid extension of involvement in the loose tissue. Depending on the location of pus—proximity of the upper or lower pole—the signs are often referred to the base of the lung and pleural cavity, or the upper right or left quadrants and paravertebral region of the costovertebral junction. A history of boils, symptoms of toxemia, marked tenderness over the costovertebral angle and high diaphragm on the affected side are for the most part constant. Roentgenograms are a decided diagnostic advantage in most cases.

#### TYPE CASES OF PERINEPHRIC ABSCESS

CASE 3—P. G., a woman, aged 24, gave a history of having had several boils on the buttocks about a month before. On May 1, 1920 she had had a mild chill and fever. The following day she had had a dull pain in the right shoulder. The appendix was removed the next day by the patient's physician, who noted no inflammation of that organ. The patient did well for a few days, and then her former symptoms returned. A large collection of pus was drained in the right flank extraperitoneally. For about two weeks she was free from pain, but she complained of chills and fever and lost 30 pounds (13.6 kg.) in weight. The abdomen was opened a second time, and nothing was found.

abscesses are not unusual after boils, but in many instances they are caused by continuity. The subcutaneous abscesses caused by streptococci are commonly metastatic. They come occasionally after peritonsillar abscess. Acute pyogenic myositis is commonly seen in the iliopsoas. Given a primary focus, however, any muscle or muscle group may become the seat of pyogenic inflammation, either spontaneously or predisposed by trauma. Acute polymyositis is possibly of *Staphylococcus aureus* nature (Schmitz<sup>5</sup>). Trauma, as in the long bones, predisposes muscles (possibly joints and kidneys) to staphylococcus infection.

Commonly patients complain of pain in the joints, either single or multiple, in the course of intermittent blood stream infection—toxic synovitis. *Staphylococcus septicemias* may give rise to single or multiple pyemic joints from which cocci are readily grown. Finally, an abscessed joint may be the only manifestation of a focal skin infection. Regarding joint conditions in general, the streptococcus plays a far more important part.

Rarely an abscess in the periprostatic tissue may be a metastatic manifestation of a carbuncle (Kretschmer<sup>13</sup>).

#### TYPE CASES OF MUSCLE ABSCESS

CASE 8—A man, about 30 years of age, entered the U S Naval Hospital at Mare Island, Calif., in 1919, with a high fever and a ligneous inflammation of the back of the neck. Three weeks previously the patient had suffered from acute rhinitis, followed by a series of "pimples" just inside the nares. About a week later he began to have slight difficulty in swallowing and three days previous to entrance his neck became painful, hard and indurated. The patient presented the picture of a toxic person unable to move his head on account of pain and stiffness. The back of the neck was of wooden consistency, swollen, hot and painful. There was no redness of the throat or bulging of the postpharyngeal wall. A slight localized discoloration in the region of the left anterolateral thigh muscles was noted. Inquiry revealed that while he was being lifted from the ambulance, he hurt his thigh on the end of a litter which was lying folded adjacent to him. The following day a small amount of pus was located by aspiration deep in the muscles of the neck. The neck was opened the next day and pus was found deep in the dorsal muscles. Culture contained *Staphylococcus aureus*. Three days later pus was aspirated from an abscess deep in the lateral rectus muscle, subjacent to the traumatized area. Culture revealed *Staphylococcus aureus*.

CASE 9—A child, aged 5, was just convalescing from a mild case of chicken-pox. The vesicle distribution was sparse, and the crusted lesions were clearing. In the second week of the disease, the child began to complain of pain over the paravertebral region (erector spinae group). Simultaneously the temperature became elevated, and there was extreme tenderness over the muscles of the back at about the level of the first lumbar vertebra on the right. Tumefaction was slight over this area, and local heat was almost imperceptible. A needle puncture revealed pus deep in the erector spinae group. The abscess was incised. Culture revealed *Staphylococcus aureus*. There was no evidence of a pox lesion in the close proximity of the abscess.

he complained of an acute pain in the left axilla, felt weak and ran a temperature of 102 F. He entered the hospital after a few days, complaining of pain in the left axilla, his afternoon temperature was high and he was weak. Physical examination revealed a normal heart. The left base showed signs of fluid up to the angle of the scapula, dulness to flatness with diminished to absent breath sounds and Grocco's sign on the right were present. Liver and spleen were not palpable. The back was blistered (medication) over the left upper lumbar region. There was tenderness over the costovertebral angle. White blood cells numbered 18,600. The urine was clear, white blood cells, double plus. Blood cultures were negative. Thoracentesis was performed, fluid was found, white blood cells, triple plus, culture negative. A second tap yielded fluid of the exudative type, white blood cells triple plus, culture negative. There were 21,800 white blood cells. The roentgen ray revealed obscure left kidney shadow, fluid at the left base, normal spine. Operation. Pockets of pus were found extending upward to the upper pole of the left kidney. Cultures from the pus contained *Staphylococcus aureus*. The roentgenogram showed no signs of fluid at the left base on discharge.

The patient was discharged well.

CASE 7—A young man entered the U. S. Naval Hospital, Mare Island, Calif., 1919, complaining of chills, fever, sweats and pain in the right upper lumbar region. There was a history of boils, the last one clearing two weeks previously. Dulness was noted at the right base, with diminished fremitus and breath sounds. The medical officer in charge of the ward aspirated thick pus by plunging the needle through the ninth interspace. Pus cultures contained *Staphylococcus aureus*. The diagnosis was empyema. The pleural cavity was opened low down in the postaxillary line. No pus was found. The needle was inserted through the lateral curve of the diaphragm in the direction of the kidney, and pus was located. It was drained extrapleurally through the diaphragm and chest wall. Cultures from the pus contained *Staphylococcus aureus*.

#### DISCUSSION

All of these cases give a history of a staphylococcus skin infection followed in a comparatively short interval of time by pus formation around the kidney region from which was isolated the same organism. In view of opinions expressed above regarding the origin of this condition, it is important to recognize the fact that all of these patients made uncomplicated recoveries by simple drainage, with but one exception. In this patient, Case 3, the kidney, after nephrectomy, appeared normal. Unfortunately, no microscopic study was made. This case is in marked contrast to Case 2 of the suppurative kidney group, which showed, in addition to free pus around the kidney, abscesses in the renal cortex.

The striking clinical features in this group are the basal chest signs caused by these infradiaphragmatic collections of pus. The observation is old and recognized. The sterile irritative exudate found in Case 4 suggested contiguous pus formation, principally because of many pus cells without demonstration of the causative organism.

#### MUSCLE ABSCESES, SUPPURATIVE JOINTS, ETC

In suppuration of the muscles, staphylococci play their rôle, not by local extension from a skin lesion, but by metastases into more distant muscle groups by way of the blood stream. Subcutaneous

or the other extremity in the cancellous substance Ochsner and Crile<sup>14</sup> believe that the organisms localize at the place where the blood flow is most sluggish, for example, on the diaphyseal side of the epiphyseal line According to Starr,<sup>15</sup> the infective agent lodges in the juxta-epiphyseal region of a long bone, passes along the line of the epiphysis to reach the periosteum, stripping this structure from the cortex and thence passes via the haversian canals to the medullary cavity The marrow is thus involved secondarily to the periosteal infection rather than by extension through the cancellous tissue, from which it is involved less frequently At a more advanced stage, large portions of the cortex become necrotic and, isolated from the living bone, lie in the pus-bathed medullary cavity as sequestra

Acute osteomyelitis is most disastrous in its sequelae if allowed to run an uninterrupted course Relief from such an acute condition is truly an emergency surgical procedure Surgeons who wait for roentgen-ray confirmation prolong the disease by months or years

It is not within the scope of this paper to comment on different surgical methods The typical case runs so true to form that there should be little diversity of opinion regarding the diagnosis The history of furunculosis or an infected skin abrasion, especially if preceded by bone trauma, is of prime importance Nasopharyngeal infections are less important (Bloomfield,<sup>16</sup> on normal flora of nasal passages) The clinical picture of toxemia accompanied by sudden severe pain in the neighborhood of a joint, with a point of local tenderness over the region of the metaphysis, are first indications of the clinical picture If allowed to continue, the characteristic tumefaction of the part develops The adjacent joint is seldom involved primarily A neighborhood serous synovitis may occur, but direct extension through the epiphysis is a late complication

#### ACUTE OSTEOMYELITIS

CASE 11—J N, a boy, aged 13, first entered the hospital in July, 1916 The child was toxic on admission, with high fever and signs of septicemia He was studied closely, and during the first two weeks many organs became involved, the principal of which were the pericardium, lungs, joints, pleura and left femur Staphylococci were repeatedly grown from the blood An operation for osteomyelitis was unfortunately delayed for two weeks, and as a consequence the boy went through months of surgical treatment for relief of the suppurating femur He returned to the outpatient department two years after the onset of the primary trouble, with a complaint of pain about the right knee, there was no swelling or redness He entered the hospital after four days' delay, where a diagnosis of osteomyelitis of the right tibia was made

14 Ochsner and Crile Surg, Gynec & Obst **31** 263, 1920

15 Starr, C S Acute Hematogenous Osteomyelitis, Arch Surg **4** 567 (May) 1922

16 Bloomfield Bull Johns Hopkins Hosp **32** 290, 1921



CASE 10—G T, a man, aged 37, about a year ago suffered from a carbuncle on the back of his neck, which lasted about a month. Shortly after healing, the patient complained of a painful swelling on the back, which was opened and pus removed. While the abscess was still draining, the patient noted a swollen, painful left thigh, which was incised and much pus removed. About this time, the left upper arm began to swell, and he was very ill with fever, pain and sweats. No surgical treatment of the bone was instigated, but pus was removed on four different occasions from the soft parts of the arm, which persisted to drain. Osteomyelitis was discovered some time later by roentgen ray, and it is reasonable to suppose that the entire disturbance of the soft tissues of the arm was contiguous to a missed osteomyelitis. The patient was operated on immediately after his admission to the hospital, and extensive sequestration of the humerus was found. The pus showed *Staphylococcus aureus* on culture.

#### DISCUSSION

In these cases it is logical to assume a metastatic abscess from the primary skin condition. Case 8 shows well the localization at the site of trauma. In Case 9 we assume a secondarily infected varicella lesion as the primary focus, with the subsequent dispersion of staphylococci to more distant parts. Such a condition is rare following chicken-pox. We are forced to assume in Case 10 a relation between the carbuncle and the multiple abscesses, for these lesions were well healed when the patient was examined, and no cultures or culture reports were available. The relationship between the carbuncle, abscesses and osteomyelitis is a well established clinical condition caused by a common organism. With the isolation of *Staphylococcus aureus* from the pus of the humerus we are probably safe in our assumption of the cause of the other conditions. Whether these abscesses were in the muscle proper or the subdermal fatty tissue is difficult to know.

#### ACUTE PYOGENIC OSTEOMYELITIS

Primary osteomyelitis does not exist as such except in a compound fracture. In the majority of cases, acute osteomyelitis is a blood-borne staphylococcus infection. (See experimental work of Rodet,<sup>2</sup> Lexer<sup>3</sup> and others.) As in the other conditions under discussion, the blood stream infection is transient in the majority of cases. However small the primary lesion, probably the majority are of a focal skin condition which offers a portal of entry for the causative coccus.

As is well known, traumatism commonly lowers the resistance of a particular bone so that the organisms more readily produce their destructive effect. It is possible that an injury may be the determining factor in localizing the site of invasion. The characteristic lesion is a panosteitis, a progressive involvement of cancellous bone, periosteum, cortex and marrow cavity in the order named. The long bones are affected far more commonly, the causative organism localizing in one

focus being the site of the original or subsequent bone infections. It has been suggested that such cases represent relative specificity of the particular strain of staphylococcus to bone lesions. This is difficult to affirm, knowing the characteristic rôle played by staphylococcus in regard to acute osteomyelitis.

The twelfth case represents a typical case of osteomyelitis, the site of focal entrance being an abrasion of the skin caused by rubbing of the shoe. Cultures from the ulcer, blood and marrow pus all contained *Staphylococcus aureus*.

The thirteenth case presents the typical history of trauma followed by symptoms of osteomyelitis and proved by operation to be of a staphylococcus nature. One need go back into the boy's history only a month to find that he suffered from a boil on the right arm, the scar of which is still obvious. This naturally brings up the question of whether or not cocci enter the cancellous bone and remain quiescent until lit up by trauma.

#### CONCLUSION

However apparently harmless skin infections appear to be, the more serious complications should always be borne in mind. To many physicians, boils in adult patients rarely bring to mind other than the examination of the urine for sugar. So characteristic are the metastatic complications of staphylococcus focal infection, particularly boils and carbuncles, that their recent occurrence should guide one in the diagnosis of certain more serious internal suppurative conditions.

240 Stockton Street

The blood culture was again positive for *Staphylococcus aureus*. Operation. Pus was removed from the periosteum and medullary cavity. The cultures contained *Staphylococcus aureus*.

CASE 12—F B, a boy, aged 12, was first seen at the Protestant orphanage on May 24, 1920, with a complaint of a sore on the right leg and a painful tender knee. He did not enter the hospital until May 29, a dangerous delay. On entrance there was noted a small purulent ulcer over the right tendo-achilles at the height of the shoe top. The right leg was swollen from the knee joint to the middle of the thigh, slightly reddened and tender. The knee joint had a small excess of fluid. The boy complained of much pain in the swollen leg. The heart was normal, temperature 39 C (102.2 F). *Staphylococcus aureus* was isolated from the blood and ulcer on the ankle. Operation. Subperiosteal pus was evacuated. Two days after operation the blood culture was negative, but the temperature remained elevated. Operation. The lateral half on the lower third of the shaft of the femur was cut away, and a purulent medullary cavity was exposed. Cultures contained *Staphylococcus aureus*. The boy remained in the hospital for a year and four months. During the interval several operations were performed for the removal of sequestra. When he was discharged his leg was still draining from a sinus 10 cm above the lateral condyle.

CASE 13—F B, a boy, on Nov 15, 1922, jumped from an elevation of 2½ feet (76.2 cm) to the ground. He did not fall, he walked home, but had pain and complained of soreness in his left leg. He returned to school the next day, but the leg was painful. He started to school the following day, but was forced to return because of swelling and great pain in the leg. He was confined to bed for two weeks before coming to the hospital. On further questioning a small scar was found on the right wrist, which the patient stated was a "sore." It was discharging, and it healed about a month before the present trouble started. On admission, the boy was markedly toxic, with a temperature of 39 C (102.2 F) and a white count of 22,000. The left lower leg was swollen from the knee to the foot, with a reddish discoloration over the middle third, especially on the medial side. Edema was marked, and pressure along the crest caused considerable pain. Operation was immediately performed. Four hundred cubic centimeters of purulent material were removed. The periosteum had been completely separated from the bone, and the marrow cavity was purulent for a distance of 10 cm. Cultures contained *Staphylococcus aureus*. The boy's leg was still draining when he was sent to another hospital fourteen days after operation. Additional surgical procedure will be necessary.

The history was obtained from the patient's mother and uncle who have a very limited knowledge of English.

#### DISCUSSION

The eleventh case is of interest because the boy was first seen when suffering from a general septicemia, the acute osteomyelitis of the left thigh being one of the many manifestations of the generalized pyemia. The blood stream infection was proved by repeated positive cultures of *Staphylococcus aureus*. The operation on the thigh was not performed early, and therefore much sequestration resulted. He has had repeated operations since. It is interesting to note that two years after the first operation he again was seen with symptoms of acute osteomyelitis of the opposite tibia, and the blood culture taken the day before the operation was again positive for *Staphylococcus aureus*. Many cases of recurrent osteomyelitis of different long bones are reported, the

with a decreased basal metabolic rate. This is further suggested by the good results obtained at times, following the administration of thyroid extract.

The foregoing description typifies the pure form of the disease, but since renal disorders are by no means always of a pure type and do not show a clear cut course, Epstein points out, this nephrosis may be associated with, or occur late in, the course of a chronic nephritis. From the therapeutic point of view, it is important to recognize this possibility. With the subsiding of the nephritis, treatment should be directed toward the nephrosis.

Since the publication of Epstein's original article and his subsequent articles<sup>2</sup> on this subject, little has appeared in the literature. Both favorable and unfavorable clinical results of the effects of feeding a high protein diet are recorded by a few observers, and there are still fewer records of detailed observations. The data of the few reports are practically all clinical, with but little accompanying findings of the blood chemistry. Of special interest are those of Kahn,<sup>3</sup> who records the essential analyses of the blood serum in a series of cases studied both before and after feeding high protein diets. Based on these observations, and those of Kerr, Hurwitz and Whipple on the stability of the blood serum protein level, of Bohm and Reiss on the concentration of serum protein made with the refractometer, and of Rowe on the effects of high protein diets on the albumin-globulin fractions, Kahn concludes that chronic nephrosis, described by Epstein, is of rare occurrence. He states that among all of his series not one case of this "metabolic" type was found, that on feeding patients suffering from "chronic parenchymatous nephritis" a high protein diet, the albumin-globulin ratio was not affected, and the edema did not diminish to the slightest extent. He further concludes that feeding such patients on such a high protein diet is a "risky undertaking." This criticism is rather severe if he refers to chronic nephrosis. The data of the four cases Kahn records, which were studied both before and after feeding, partly bear out his views. An analysis of the data, however, shows that in none of these cases do the chemical findings correspond to the Epstein type of chronic nephrosis. Table 1 shows the values Kahn found in these cases. Since no case of this "metabolic" type was found, it is apparent that the results obtained are not surprising.

Numerous observations made in this hospital corroborate one view held by Kahn, namely, the uncommon occurrence of chronic nephrosis. The case recorded here is the first noted during a routine examination of all cases of a renal nature admitted during the last three years.

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2 Epstein, A. A. Further Observations on the Nature and Treatment of Chronic Nephrosis, *Am J Med Sc* **163** 167, 1922.

3 Kahn, Max. The Protein and Lipin Content of Blood Serum in the Nephritides, *Arch Int Med* **25** 112, 1920.

# A CONTRIBUTION TO THE BIOCHEMISTRY AND TREATMENT OF CHRONIC NEPHROSIS (EPSTEIN)\*

I M RABINOWITCH, M D, AND M C C CHILDS, M D  
MONTREAL, CANADA

Following many observations made—clinical and chemical—in various forms of renal disorders, Epstein,<sup>1</sup> in 1917, reported what he regarded as a clinical and pathologic entity, called by him a chronic nephrosis, which clinically simulates, although in many respects it differs from, the commonly known forms of chronic parenchymatous nephritis. Briefly, this condition is regarded as one of a metabolic nature, in which the renal and other clinical manifestations are concomitant or secondary in point of development and importance. Both the clinical and laboratory findings are characteristic in the pure form of the disease. Its origin is slow, insidious and of unknown etiology. The first intimation the patient may have of the disease is the pallor and evidence of edema. The course is protracted. Objectively, there is a general anasarca, oliguria and absence of increase in the blood pressure and cardiac hypertrophy. It occurs, as a rule, in relatively young people. The urine shows a high specific gravity, a marked albuminuria with or without casts, and the absence of blood elements. The blood serum has a milky appearance, its total protein content is low, the albumin-globulin ratio is reversed, and the globulin may be both relatively and absolutely increased. The blood shows a high cholesterol content.

The treatment recommended—a high protein diet—is based on the theoretical conception of the cause of the edema. The latter is attributed to a disturbance between the intracapillary pressure and osmotic force of the blood. This idea is based on the observation of Starling, on the osmotic effect of the blood proteins. The marked loss of protein, or colloid content of the blood, characteristic of the disease, lowers the osmotic pressure of the blood, and on account of this the osmotic force of the tissue fluids becomes relatively increased. This leads to the attraction of fluid to the tissues, with the production of edema.

The diet is essentially of a high protein, low carbohydrate, low fat nature. By this means it is hoped that the high protein content will replace the protein lost in the urine, and the low fat and low carbohydrate may influence the body to utilize all the protein ingested and the excess lipoids already present in the blood.

That this disease is a metabolic disturbance is suggested by the lipidemia, and in some cases by the presence of a hypothyroid state.

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\* From the department of metabolism of the Montreal General Hospital.

1 Epstein, A. A. Concerning the Causation of Edema in Chronic Parenchymatous Nephritis, *Am J Med Sc* **154** 638, 1917.

RCD and heart sounds were the same as during the former admission. The complete analyses of blood, urine, etc., are recorded in Tables 2, 3 and 4. The treatment and laboratory analyses will be discussed below. The patient's weight on admission was 171½ pounds (77.9 kg), and on discharge, 123 pounds (55.7 kg). The blood pressure on discharge was systolic, 138, diastolic, 76. On April 19, 1923, the patient was discharged in a much improved condition. There was no edema present.

#### COMMENT

The tables give the complete laboratory data obtained. Tests made during the early period in the hospital showed a marked impairment in the renal function. The renal test meal showed a marked salt, water and nitrogen retention, a fixation both in the density and volume in the periodic specimens, and a diminished concentration of the nitrogen of the night urine. The excretion of total solids, and the day-night solids ratio also showed impairment. This is also shown by the increase in the concentration of urea nitrogen in the blood and a diminished concentration of urine urea following the ingestion of 15 gm of urea. The analysis of the blood serum proteins, Table 2, showed a much diminished concentration of total protein and a reversed albumin-globulin ratio. The cholesterol content of the blood, Table 2, was greatly increased. Correlating the foregoing data with the clinical history of the onset and the physical examination, the picture is that of chronic nephritis, associated with chronic "nephrosis."

During this period of observation the patient was on a salt free, low protein and restricted fluid diet, with the exception of the day on which the renal test meal was given. On this diet there was a general clinical improvement, as occurred during the former period in the hospital—a diminution in the amount of edema and a fall in the blood pressure to systolic, 120, diastolic, 70. The weight dropped to 123 pounds, but the total protein content of the blood serum and the albumin-globulin ratio were little altered, and there was still edema of the legs and ankles.

Based on these observations—the persistence of edema—the unchanged chemical state of the blood and the unsuccessful treatment of the patient during the first admission to the hospital—a high protein diet approximating that described by Epstein was commenced. The data shows the progress made. The results of the renal test meal on admission and prior to discharge are of interest. The latter shows a marked improvement in function. There is a normal water balance, only a slight salt retention and a normal nitrogen balance. The variation in volume and density of the periodic specimen is normal. The excretion of total solids is increased, above that found on admission, on a diet of the same total solid content. Improvement is also shown by the fall in the cholesterol content of the blood to near the normal level (normal 140 to 180), and by the increased concentration of urine urea following the ingestion of urea. That some impairment is still

Our case does not represent the pure form described by Epstein, but corresponds to a nephrosis, probably superimposed on, or associated with, a chronic nephritis. Epstein points out that such cases as this mixed type are not uncommon in his experience. The presence of a nephrosis in our case is demonstrated by the chemical analyses of the blood (high cholesterol and low protein content, and reversal of albumin-globulin ratio), the clinical history of the onset and course of the case following the treatment with a high protein diet. The object here is to present briefly the clinical history and laboratory data obtained throughout a period of six months.

TABLE 1—*Effect of Feeding a Protein Rich Diet in Cases of Parenchymatous Nephritis*

Case	Period	Total Protein	Albumin	Globulin	Globulin, Percentage
4	Before	4.24	2.93	1.31	31
	After	5.27	3.59	1.68	32
8	Before	7.60	4.26	3.34	44
	After	7.75	4.50	3.25	42
9	Before	5.76	3.75	2.01	35
	After	6.12	3.92	2.20	36
11	Before	6.09	1.14	1.95	32
	After	6.37	4.46	1.91	30

#### REPORT OF A CASE

*History*—A woman, aged 37 years, was first admitted on Oct 23, 1922, to the medical wards of the Montreal General Hospital, in the service of Dr F G Finley. She was apparently in good health until on Oct 1, 1922, when she first noted swelling of both feet. There were no other complaints. The family and personal history were irrelevant.

*Physical Examination*—The patient appeared comfortable in any posture. There was marked pallor. The ocular and buccal mucosae were pale. The legs were edematous. The blood pressure was systolic, 210 mm of mercury, diastolic, 116 mm of mercury. R C D  $\frac{\text{III}}{3/10 \text{ cm}}$  (R C D refers to the areas of relative cardiac dulness found on percussion). A systolic murmur at the apex replaced the whole of the first sound. The electrocardiogram was normal. Breath sounds were vesicular. Many loud sibilant rhonci were heard all over the chest. In the fundi there was degeneration of the arteries but no exudate or hemorrhage. The patient had marked albuminuria and there were many casts. The specific gravity was 1.030.

The renal test meal showed a tendency toward fixation in density and volume in the periodic specimen, and a nocturnal polyuria. The blood urea nitrogen was 24 mg per 100 cc creatinin 1.5 mg. The urea concentration of the urine following ingestion of 15 gm of urea was 1.29 per cent after the first hour and 2.04 per cent after the second hour. There were 3,200,000 red blood cells, 7,800 white blood cells and 50 per cent hemoglobin. The usual treatment, including a salt free, low protein and restricted fluid diet, and purgation, was given. Throughout the course in the hospital, the temperature was normal. On Nov 1, 1922, the patient was discharged slightly improved. There was still some edema present about the ankles. The blood pressure was systolic, 180, diastolic, 100.

*Second Admission*—The patient was readmitted on Feb 3, 1923, with a history of being well only three days after discharge from the hospital. On admission the positive findings were marked pallor, general anasarca, oliguria and good appetite. The blood pressure was systolic, 214, diastolic, 140.

present, is shown by the persistence in the increased amount of blood urea nitrogen, a nocturnal polyuria in the renal meal, and diminished day-night ratio of excretion of solids. Accurate data of the effect of the diet on the salt, water and nitrogen balance were not recorded early in the period of observation. To obtain data on this phase of the subject, the patient was placed under routine metabolism orders. All food and fluids were prepared in and served from the metabolism diet kitchen. The collection of urine was accurately controlled. The total salt, water and nitrogen content of the diet, including the salt and water content of the solid food, were calculated from the Atwater-Bryant food tables. A few residues were calculated and subtracted on the same basis. A constant diet was given, and it will be noted in Table 9 that the patient had, as she stated, a good appetite, little residue being recorded in only a few instances during the entire period of observation. It will be noted also that although sufficient salt was given daily to make the food palatable, this did not affect the favorable progress of the case and the end result. The salt was not only totally eliminated, but during the entire period in which records were kept, forty days (from March 8 to April 16) there was a total excretion of 47 gm of salt (calculated as sodium chlorid) in excess of that ingested. This is contrary to expectation, if this is a case in which the only lesion present is that in which the kidneys are unable to excrete salt. This loss of salt may partly explain the clinical result. The patient was discharged on April 19, 1923, weighing 123 pounds, the edema had completely disappeared. Since the weight remained the same after the institution of the high protein diet in spite of the complete absence of edema, it appears reasonable to assume that the patient actually gained real tissue weight on this diet. This corresponds with the improved clinical appearance of the patient. The various tables show that with the clinical improvement there was practically a return to normal in the protein composition of the blood serum, including the total amount and albumin-globulin ratio. The data also show that the high protein diet did not at any time react unfavorably.

#### SUMMARY

A case of chronic nephritis associated with a chronic nephrosis is recorded. The usual treatment of chronic nephritis, including restriction of salt water and nitrogen, caused improvement to a certain stage, which became stabilized, the edema still persisted. Following the institution of a high protein diet there was no evidence of a further increase in the nonprotein nitrogenous elements in the blood and no clinical symptoms suggestive of any harmful effects. The end result was a marked improvement in the clinical picture, with a complete disappearance of the edema. Improvement was also shown by the chemical state of the blood and renal function tests.



TABLE 2—Blood Serum Protein Estimations

Date	Total Protein	Albumin	Globulin	Globulin Percentage	Cholesterol Gm per Cent
February 11	3.9	1.30	2.60	66.6	0.781
February 27	3.7	1.45	2.25	61.0	
March 18	5.8	2.88	2.98	51.3	0.426
April 17	7.72	4.67	3.05	39.6	0.201

TABLE 3—Kidney Function

Date	Blood			Urine, Urea Concentration, Percentage	
	Urea Nitrogen Milligrams per 100 C c	Creat. min. Milligrams per 100 C c	Sodium Chlorid Percentage	First Hour	Second Hour
February 3	52	1.46	0.6682		
8	22	1.50			
12	20	1.50		0.96	1.00
21	28	1.58		0.78	0.84
March 7	52	2.0			
9			0.6188		
15	36	1.53	0.6188		
19	48				
21	54	1.62			
April 9	50		0.5445		
18	55	1.42	0.6105	1.41	2.00

TABLE 4—Salt, Nitrogen and Water Balance

Date	Intake			Output		
	Water	Sodium Chlorid	Nitrogen	Water	Sodium Chlorid	Nitrogen
March 8	1,750	6.0	15.6	550	11.6	9.0
9	1,750	6.0	15.6	950	9.2	8.9
10	1,750	6.0	15.6	1,020	13.9	6.3
11	1,750	6.0	15.6	870	12.6	9.2
12	1,750	6.0	15.6	950	14.0	11.1
13	1,750	6.0	15.6	1,250	5.5	13.2
14	1,750	6.0	15.6	1,000	6.0	16.8
15	1,750	6.0	10.2	1,350	5.4	9.8
16	1,750	6.0	15.6	1,475	7.0	10.0
17	1,750	6.0	15.6	1,400	5.9	11.0
18	1,750	6.0	15.6	1,380	7.1	14.5
19	1,750	6.0	15.6	1,770	4.9	14.6
20	1,750	6.0	15.6	1,320	5.8	16.6
21	1,750	6.0	15.6	1,350	5.9	14.8
22	1,750	6.0	15.6	1,125	6.2	9.5
23	1,750	6.0	15.6	1,260	5.0	15.1
24	1,750	6.0	15.6	1,120	4.0	12.9
25	1,260	6.0	15.6	900	5.0	12.3
26	1,750	6.0	15.6	1,230	5.9	8.5
27	1,750	6.0	15.6	1,260	7.2	14.3
28	1,750	6.0	15.6	1,400	5.0	15.6
29	1,750	6.0	15.6	1,000	3.6	16.7
30	1,750	6.0	15.6	1,350	5.4	10.3
31	1,750	6.0	15.6	1,400	6.1	13.7
April 1	1,200	6.0	15.6	980	5.8	12.54
2	1,750	6.0	15.6	1,500	7.8	12.1
3	1,750	6.0	13.8	1,370	6.5	14.6
4	1,250	6.0	15.6	1,370	6.0	14.3
5	1,750	6.0	15.6	1,240	6.9	15.1
6	1,750	6.0	15.6	1,030	5.7	12.6
7	1,750	6.0	15.6	1,125	7.2	16.1
8	1,750	6.0	15.6	1,100	4.4	15.8
9	1,600	6.0	15.6	1,255	6.2	17.8
10	1,200	6.0	11.9	1,325	6.3	10.1
11	1,750	6.0	15.6	1,070	4.7	14.0
12	1,750	6.0	15.6	1,260	6.0	16.0
13	1,750	6.0	15.6	1,100	7.4	13.3
14	1,750	6.0	15.6	1,250	7.0	12.4
15	1,750	Renal meal day				
16	1,750	6.0	15.6	1,125	7.2	13.3

In Table 1 the collected clinical data concerning the patients is given. In Table 2 the data of the blood oxygen analyses and basal metabolism determinations is given, and in Table 3 data concerning the control subjects.

In reviewing the literature, it was found that Bondi and Mueller<sup>4</sup> in 1909 studied the systolic output of the heart by an arm plethysmograph method, and included seven diabetic persons among a group of

TABLE 1—*Oxygen Unsaturation and Clinical Data in Patients with Arteriosclerosis and with Diabetes*

Patient	Age	Habitus	Duration of Diabetes	Arteriosclerosis	Sugar in Urine	Blood Sugar Percentage	Blood Pressure	Oxygen Unsaturation, % by Volume	Other Diagnoses
1	48	Normal	18 mo	Slight	0	0.212	122/ 72	12.07	None
2	44	Obese	12 mo	None	0	0.150	140/ 92	15.10	None
3	42	Normal	7 yr	None	0		120/ 84	7.15	None
4	39	Obese	30 mo	None	0	0.177	116/ 80	12.39	None
5	65	Normal	12 mo	Moderate	0	0.140	170/ 90	7.49	None
6	54	Normal	6 mo?	None	0	0.130	155/ 99	7.97	Chronic myocarditis
7	66	Slight wasting	2 yr	Slight	Trace	0.110	124/ 70	11.45	Neuritis
8	54	Normal	6 yr	Moderate	0	0.080	240/130	9.00	Angina pectoris
9	38	Normal	?	None	0.8%	0.090	165/120	7.02	None
10	57	Wasted	2 yr	Slight	0	0.250	124/ 72	4.57	None
11	43	Wasted	4 yr	None	0.37%	0.160	142/100	1.80	None
12	71	Wasted	?	Definite	Trace	0.180	185/110	9.98	None
13	51	Normal	14 yr	Slight	Trace	0.140	130/ 70	9.55	None
14	42	Normal	4 yr	None	Trace	0.110	100/ 58	8.49	None
15	54	Slight wasting	3 yr	Moderate	0	0.120	130/ 84	10.93	None
16	62	Wasted	1 yr	Moderate	0	0.140	155/ 90	7.49	Active pulmonary tuberculosis
17	49	Obese	4 mo	None	0	0.140	130/ 80	7.63	None
18	18	Wasted	4 mo	Very slight	1.3%	0.290	118/ 80	4.56	Active pulmonary tuberculosis
19	13	Wasted	13 mo	None	2.94%	0.250	85/ 45	8.58	None
20	48	Obese	?	Very slight	0		150/125	6.45	Chronic myocarditis
21	36	Wasted	5 yr	None	0.37%	0.190	110/ 75	9.22	Cataract
22	21	Wasted	18 mo	None		0.230	92/ 72	7.24	None
23	23	Thin	3 mo	None	1.2%	0.195	118/ 90	9.84	None
24	33	Wasted	14 mo	Moderate	0	0.239	76/ 40	2.41	None
25	53	Obese	5 yr	None?	0	0.174	148/ 99	11.87	None
26	52	Normal	5 yr	Slight	0.75%	0.210	115/ 80	5.71	None
27	38	Wasted	9 mo	Slight	0	0.336	100/ 64	12.50	None
28	28	Wasted	5 mo	None	5.8%	0.253	105/ 70	7.32	None
29	50	Obese	3 mo?	None	0	0.157	148/100	10.85	None
30	50	Wasted	4 yr	Slight	0	0.195	128/ 80	12.36	None
31	60	Normal	3 yr	None	0.16%	0.183	145/ 80	12.17	None
32	22	Normal	30 mo	None	0	0.276	104/ 76	13.65	None
33	57	Obese	9 yr	Moderate	0	0.151	165/ 80	12.06	Diabetic ulcer
34	62	Obese	?	Slight	0	0.265	134/ 60	8.36	Duodenal ulcer

other patients. By this method three of the seven diabetic patients had a smaller systolic output than normal. In 1922, E. Koch<sup>5</sup> studied the rapidity of the circulation by injecting a dye into the vein of one arm and noting the time before its appearance in the vein of the opposite arm. In the five cases of diabetes included among a large number of miscellaneous cases, the rate was slower than normal.

<sup>4</sup> Bondi, S., and Mueller, A. *Deutsch Arch f klin Med* **97** 569, 1909.

<sup>5</sup> Koch, E. *Deutsch Arch f klin Med* **140** 30, 1922.

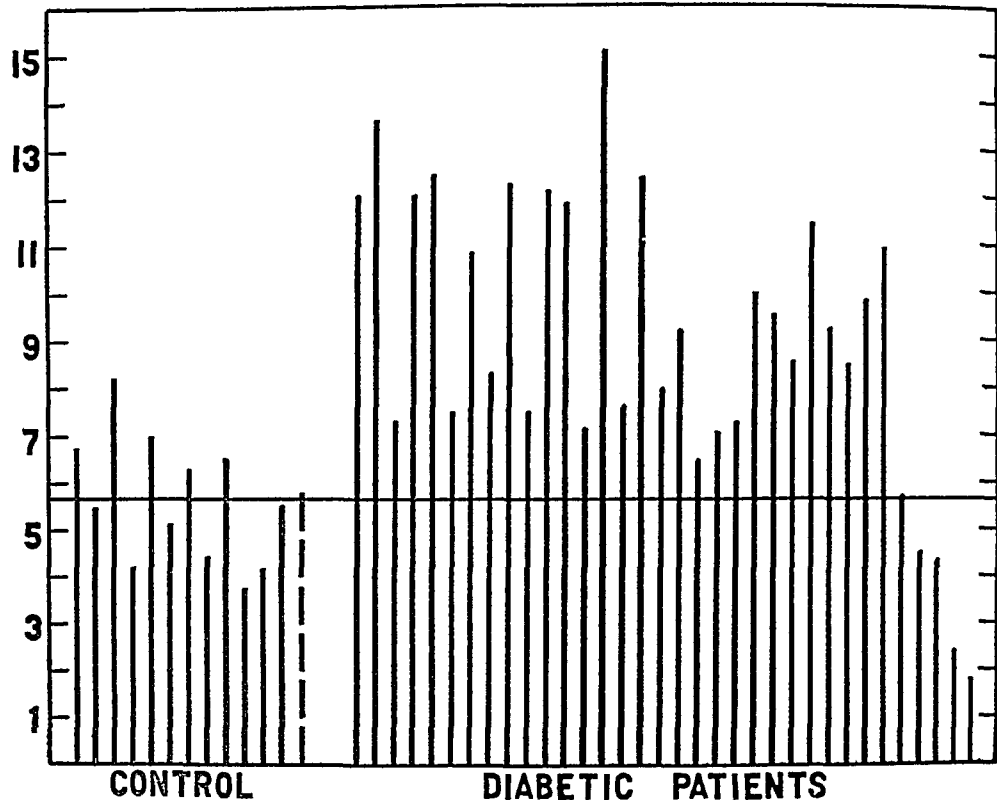


Fig 1—The vertical lines represent the oxygen unsaturation of the venous blood in per cent by volume. The broken line in the control group represents the average normal found by Lundsgaard. The horizontal line is at the average height of the control group.

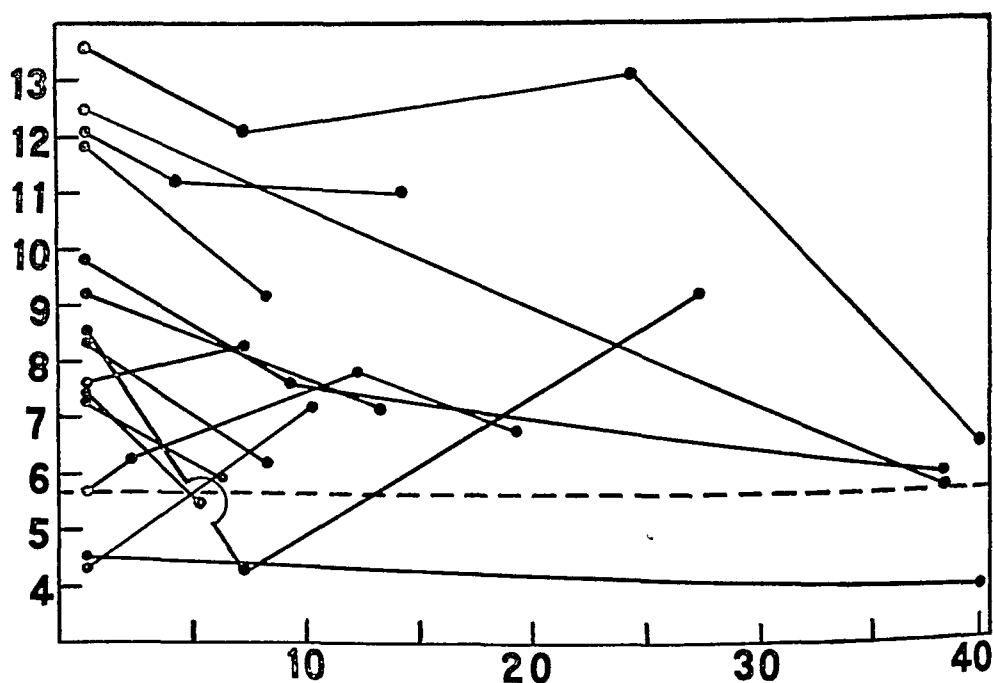


Fig 2—Venous oxygen unsaturation in per cent by volume of fourteen diabetic patients who had two or more determinations during the course of treatment. The time is charted in days along the base line. The interrupted line indicates the average normal.

In twenty-nine of the patients determinations of the basal metabolism were made, many of them in connection with a study of insulin being carried on by Dr Fitz and Dr Murphy. These determinations were made in duplicate by Miss G Kauffmann, using the Tissot method, the expired air being analyzed in the Haldane apparatus, and the oxygen consumption per minute thus accurately ascertained. In these patients, immediately after the completion of the basal metabolism determination, while the patient was still under basal conditions, samples of blood were drawn without stasis and under oil from the antecubital vein and from the radial artery, and analyzed for oxygen content and oxygen capacity. I then indulged in the luxury of calculating a figure for the blood flow on the basis of these figures, realizing fully the fallacy of attempting to calculate the blood flow of the body

TABLE 3—Data Concerning Control Subjects

Subject	Diagnosis	Oxygen Capacity, % by Volume	Venous Oxygen Content, % by Volume	Arterial Oxygen Content, % by Volume	Oxygen Saturation, % by Volume	Basal Metabolism Percentage	Oxygen Intake per Minute	Surface Area, Square Meters	Index of Blood Flow per Minute, Cc
A	Normal	20.62	16.39	20.84	4.23	0	235	1.68	3,143
K	Normal	17.26	10.50	17.22	6.76	+11	218	1.53	2,120
E	Normal	17.85	12.68	17.40*	5.17	— 9	167	1.38	2,828
G	Normal	20.55	16.08	20.04*	4.61	— 7	216	1.92	3,244
W	Arthritis	17.93	11.47	17.48*	6.46	+ 7	230	1.54	2,681
C	Inactive pulmonary tuberculosis	20.23	14.71	19.38	5.62	+12	295	1.91	3,642
P	Constipation	21.29	14.96	20.76*	6.83	— 6	282	1.73	2,545
R	Acromegaly	17.51	13.73	16.98	3.78	+14	269	1.74	4,597
J	Adenoma of thyroid	19.29	15.10	18.75	4.19	0	235	1.63	3,915
D	Duodenal ulcer	18.18	9.94	18.53	8.21	— 4	236	1.83	1,501
W	Normal	19.03	12.32		6.71				
S	Normal	18.41	12.88		5.53				
F									
H									

\* The arterial blood was not obtained in these instances, but was assumed to be 97.5 per cent saturated.

by using factors in which the utilization of oxygen from blood in only one part of the body (the arm in this case) is included. The oxygen consumption was divided by the difference between the oxygen contents of the arterial and the venous blood, and, since the oxygen consumption is proportional to the surface area, the figure obtained was divided by the surface area in order to compare persons of different sizes more accurately. Naturally, the figures thus obtained did not actually represent the total blood flow. They may, however, represent a rough index of the volume of the circulation in the arm.

The results of these calculations showed a striking difference between the twenty-nine diabetic and ten control subjects. Of the diabetic persons, all but three had a figure for the blood flow which was lower than the average normal, and the average figure for all the diabetic persons was 1827 cc, as compared with 3024 cc for the

TABLE 2—Blood Oxygen Analyses and Basal Metabolism

Patient	Oxygen Capacity, % by Volume	Venous Oxygen Content, % by Volume	Arterial Oxygen Content, % by Volume	Oxygen Unsaturation, % by Volume	Basal Metabolism Percentage	Oxygen Intake per Minute	Surface Area, Square Meters	Pulse Rate	Index of Blood Flow per Min., Cc
1	21.52	9.45	20.45	12.07	— 4	240	1.82	68	1,199
2	22.93	7.83	22.03	15.10	— 1	285	2.11	91	886
3	20.37	13.22	19.57	7.15	+ 2	236	1.71	85	2,173
4	18.70	6.31	18.23*	12.39	+ 4	201	1.51	89	1,117
5	20.99	13.50	20.47*	7.49	— 6	220	1.83	78	1,725
6	20.53	12.56	20.49	7.97	+ 4	205	1.62	64	1,596
7	20.05	8.60	19.60	11.45	—21	161	1.64	82	893
8	17.78	8.58	17.34*	9.20	— 3	250	1.95	60	1,464
9	22.54	15.52	22.96	7.02	+12	286	1.83	90	2,101
10	18.57	14.00	18.62	4.57	— 1	170	1.38	86	2,667
11	16.49	14.69	16.11	1.80	—27	150	1.50	64	7,042
12	18.10	8.12	17.54	9.98	— 5	188	1.44	69	1,165
13	17.15	7.60	17.39	9.55	—13	188	1.64	50	1,171
14	17.40	8.91	16.96	8.49	—12	216	1.80	61	1,491
15	19.22	8.29	18.78	10.93	—14	206	1.81	55	1,085
2 days later	18.49	5.88	18.03*	12.61	—14	206	1.82	55	934
16	18.52	11.03	18.06*	7.49	(+10)†	(201)	(1.53)		(1,869)
5 days later	18.66	13.17	17.41	5.49	+10	201	1.53	77	2,444
17	20.92	13.32	20.40*	7.60	(— 6)	(204)	(1.70)		(1,200)
7 days later	19.13	10.89	17.93	8.24	— 6	204	1.70	74	1,705
18	18.11	13.55	17.51	4.56	+ 3	194	1.40	67	3,493
48 days later	17.17	13.22	16.93	3.95	— 5	175	1.38	87	3,418
19	17.95	9.37	17.95	8.68	—40	113	1.07	68	1,231
7 days later	16.75	12.39	16.75	4.36	—46	117	1.11	60	2,401
27 days later	14.88	5.59	14.80	9.29	—35	124	1.10	54	1,224
20	20.84	15.47	20.32*	5.87	+28	303	1.85	124	3,377
15 days later	20.65	14.20	20.13*	6.45	— 7	221	1.85	93	2,015
21	19.21	14.10	19.31	5.11	+13	249	1.57	75	3,044
12 days later	17.36	8.14	17.04	9.20	—16	183	1.57	57	1,310
25 days later	16.78	9.56	16.36*	7.20	—16	187	1.60	57	1,719
22	18.11	13.78	18.66	4.33	— 1	160	1.25	77	2,623
10 days later	17.68	10.44	17.58	7.24	— 6	159	1.28	74	1,740
23	19.71	9.87	19.22*	9.84	(—24)	(153)	(1.55)		(1,056)
9 days later	18.24	10.60	18.24	7.64	—24	153	1.55	59	1,292
40 days later	15.50	9.49	15.28	6.01	—21	157	1.55	67	1,750
5 mos later	17.40	10.23	17.28	7.17	—25	141	1.47	63	1,361
24	18.68	16.27	18.21*	2.41	(—38)	(123)	(1.52)		(4,171)
9 days later	17.04	12.36	16.57	4.68	—38	123	1.52	54	1,922
40 days later	14.72	11.50	14.31	3.22	—20	154	1.52	61	3,605
50 days later	17.68	14.45	17.19	3.23	—15	157	1.49	65	3,546
5 mos later	16.23	13.36	16.19	2.87	—13	168	1.50	65	3,957
25	18.97	7.10	18.50*	11.87	(0)	(261)	(2.10)		(1,090)
8 days later	18.95	9.77	17.86	9.18	0	261	2.10	67	1,536
26	19.61	13.90	19.12*	5.71	(—23)	(160)	(1.59)		(1,928)
2 days later	18.89	12.67	18.42*	6.22	(—23)	(160)	(1.59)		(1,750)
12 days later	17.73	9.92	17.31*	7.81	(—23)	(160)	(1.59)		(1,365)
20 days later	17.11	10.29	16.77	6.82	—23	160	1.59	63	1,553
27	16.68	4.18	16.26*	12.50	(— 1)	(206)	(1.48)	(74)	(1,152)
38 days later	16.87	11.10	16.45*	5.77	—12	188	1.55	64	2,267
28	19.09	11.77	18.61*	7.32	(— 4)	(204)	(1.53)		(1,950)
6 days later	19.49	13.53	19.00*	5.96	— 4	204	1.53	61	2,437
29	19.71	8.86		10.85					
30	17.36	5.00		12.36					
31	21.21	9.04		12.17					
32	19.22	5.67	18.74*	13.65	(— 5)	(230)	(1.73)		(1,010)
7 days later	20.26	8.24	19.75*	12.02	— 5	230	1.73	51	1,155
22 days later	18.40	5.35	17.95*	13.05	(— 5)	(230)	(1.73)		(1,050)
5½ mos later	17.91	11.41	17.46*	6.50	+ 9	272	1.78	62	2,526
6 mos later	17.90	11.79	17.45*	6.11	— 9	227	1.77	57	2,266
33	19.68	7.62		12.06					
4 days later	18.91	7.69		11.22					
14 days later	18.76	7.78		10.98					
34	20.98	12.62		8.96					
8 days later	14.54	8.32		6.22					

\* The arterial blood was not obtained in these instances, but was assumed to be 97.5 per cent saturated

† The determinations of the basal metabolism were not always made each time blood samples were taken in which case figures from other determinations on the same patient were used in the calculations. These figures are enclosed in parentheses

# GASTRIC SECRETION IN RESPONSE TO DUODENAL FEEDING \*

A L GARBAT, M D

Associate Visiting Physician and Bacteriologist, Lenox Hill Hospital  
NEW YORK

The treatment of gastric diseases by duodenal alimentation attempts to put the stomach at rest from its motor activity, as well as from its secretory action. It became of interest to the writer to determine to what extent one can actually eliminate the function of the gastric epithelia. With this object in view, experiments by means of two duodenal tubes were begun on July 7, 1921, and continued to the present time. I mention this date, because recently Heller<sup>1</sup> employed the same principle for other work.

## TECHNIC

The Einhorn tube was first allowed to pass into the duodenum in the usual way. After it was definitely proved in place and duodenal alimentation had been successfully carried out, another duodenal tube was swallowed, but not allowed to pass out of the stomach. It was at times difficult to have this second tube rest at the most dependent portion of the stomach. One must be certain that this is the case, as otherwise aspiration will not bring forth the secretions. At times it required the roentgen rays to visualize its proper position. Then, too, it is often necessary to change the posture of the patient from reclining to sitting, or vice versa, or from one side to another, to enable proper suction. A tight asbestos aspirating syringe is employed. In spite of all these precautions, complete emptying of the stomach by aspiration is well nigh impossible, because of the changing position of the tube.

## DUODENAL ALIMENTATION

The feedings took place every two hours, and consisted of 7 ounces (200 gm) of milk, two eggs, one-half dram (1.95 gm) of lactose, one square of butter and a pinch of salt. The regular Einhorn duodenal outfit was used, and the aim was always that each feeding should not take less than twenty minutes. As a rule, seven feedings a day were given—at 8, 10, 12, 2, 4, 6 and 8 o'clock, and twice a day 500 cc of warm saline were allowed to enter the duodenal tube by the drip method.

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\* Read at the American Gastro-Enterological Association, Atlantic City, April 30, 1923.

\* From the laboratory and medical division of the Lenox Hill Hospital Service of Dr J Kaufmann.

<sup>1</sup> Heller, E P. Employment of Two Duodenal Tubes in Gastro-Enterology, J A M A 80 31 (Jan 6) 1923.

normal subjects, a reduction of 40 per cent (Fig 3) Ten of the diabetic persons had a basal metabolism of from 17 to 40 per cent below normal, with a correspondingly low oxygen consumption This would account for part of the lowering of the figure in these ten subjects, but not entirely, because seven of them had a definitely increased oxygen unsaturation in the venous blood Two of them, with basal metabolisms of —38 and —27, had oxygen unsaturations which were markedly lower than normal, so that the figure for the blood flow was actually greater than normal The low metabolic rates in these patients were presumably due to the prolonged period of undernutrition

Arteriosclerosis is undoubtedly the factor of prime importance in the production of diabetic gangrene, but it is interesting to speculate

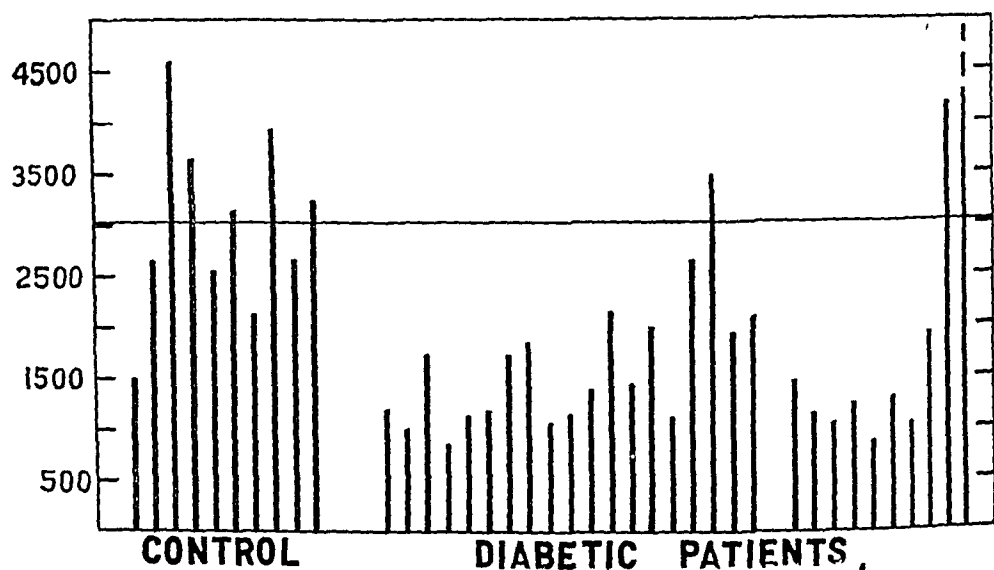


Fig 3—The vertical line represents the figures obtained in calculating the index of minute volume of blood flow in the arm The horizontal line is at the average height of the control group The group of diabetic patients at the extreme right is composed of those having basal metabolic rates from 10 to 40 per cent below normal

as to the possible relationship between the increased oxygen unsaturation, independent of arteriosclerosis, and the susceptibility of diabetic persons to gangrene and infections of all sorts

#### SUMMARY

1 The average venous oxygen unsaturation of thirty-four diabetic patients was found to be 59 per cent greater than the average normal

2 This increase in the venous oxygen unsaturation would seem to indicate a slow blood flow through the arm in diabetic patients However, this cannot be definitely stated to be true The data concerning the blood oxygen is offered merely as an addition to the mass of slowly accumulating facts known about diabetes mellitus

In order to show that this gastric response after duodenal feeding was not accidental or exceptional, eight additional examinations were made on different days at different times and at different intervals after the duodenal feedings, and at no time was the stomach found free of secretion. As is seen in Table 3, one could aspirate quantities varying from 3 to 75 c c, and with acid contents as high as free hydrochloric acid 100 and total acidity of 110, figures much higher than those noted after the Boas-Ewald meal.

This patient suffered from an irritative form of gastric disorder, but of a moderate type and not the more marked form usually designated as alimentary hypersecretion.

TABLE 3—*Secretion After Duodenal Feeding*

Hour of Duodenal Feeding	Time of Gastric Aspiration Before or After Duodenal Feeding	Amount of Secretion	Free Hydrochloric Acid	Total Acidity
July 13, 1921, 10 a m (milk egg mixture)	5 min before	15 c c	8	28
11 a m (saline solution)	30 min after	10 c c	50	80
	50 min after	30 c c	32	56
12 p m (milk egg mixture)	5 min before	15 c c	80	100
	2 hours after	8 c c	40	68
	3½ hours after	3 c c	30	60
4 p m (milk egg mixture)	30 min after	12 c c	66	88
	1½ hours after	13 c c	100	110
July 14, 1921, 8 10 p m (milk egg mixture)	25 min after	45 c c	80	94
	50 min after	30 c c	62	74
	1 hr 20 min after	22 c c	86	100
4 p m (milk-egg mixture)	30 min after	45 c c	80	94
10 30 a m (milk egg mixture)	30 min after	75 c c	46	56
9 15 p m (milk-egg mixture)	30 min after	17 c c	56	60

TABLE 4—*Findings After Employing the Two Tube Experiment*

Duodenal Feeding at 4 to 4 20	Amount	Free Hydrochloric Acid	Total Acidity
Gastric aspiration just before feeding	5 c c	0	20
Gastric aspiration at 4 30 p m, 10 min after	59 c c	52	66
Gastric aspiration at 5 00 p m, 40 min after	35 c c	40	62
Gastric aspiration at 5 30 p m, 70 min after	20 c c	56	74
Gastric aspiration at 6 00 p m, just before next feeding	5 c c	0	4
Total	149 c c		
Duodenal Feeding at 6 to 6 20 p m			
Gastric aspiration at 6 30 p m showed	105 c c	46	60
Gastric aspiration at 7 00 p m showed	28 c c	30	42
Gastric aspiration at 7 30 p m showed	5 c c	60	70
Gastric aspiration at 8 00 p m showed	3 c c	4	8
Total	141 c c		

Similar experiments were repeated on another patient also with a moderate gastric secretion.

CASE 2—A man, aged 54 years, suffered at varying intervals for eight years with burning pain in the epigastrium, which came on from one to three hours after eating and was relieved by taking food or bicarbonate of soda. In addition, he had acid eructations, heartburn, hiccups and frequent vomiting of sour material. He had lost 20 pounds (9 kg) during his illness, but the greater part in the last three weeks. Roentgen-ray examination showed marked gastropexia and deformity of the cap, which, however, was not constant. On aspiration three-fourths hour after the Boas-Ewald test meal, 151 c c of gastric contents were obtained, with a free hydrochloric acid reading of 31 and total acidity of 58.



## REPORT OF CASES

CASE 1—H W., a salesman, aged 35, admitted to the service of Dr J Kaufmann at the Lenox Hill Hospital on June 29, 1921, had complained for five months of a burning feeling and bloated sensation in the epigastrium associated with acid eructations and belching. These disturbances would come on about an hour after eating and continue indefinitely until the next meal, when he would again be relieved for a short time by food. At night he had a gnawing pain in the pit of his stomach. The bowels were constipated. He had lost 16 pounds (7.25 kg) in weight in five months. He was an asthenic type with a low blood pressure (systolic, 104, diastolic, 70). The urine was normal. A fractional analysis of the gastric contents was made after a Boas-Ewald test meal and showed hyperacidity (Table 2). Red blood cells were noted microscopically in the gastric contents. Roentgen-ray examinations were unsatisfactory, because the patient did not hold his breath properly.

TABLE 1—*Result of Simultaneous Duodenal Feeding and Suction on the Gastric Tube*

	Amount of Gastric Juice Aspirated	Free Hydrochloric Acid	Total Acidity
Immediately after the first 25 c c of duodenal feeding	48 c c	46	58
15 minutes later	8 c c	58	74
30 minutes later	30 c c	62	76
45 minutes later	12 c c	18	40
1 hour later	14 c c	34	56
1½ hour later	14 c c	42	60
2 hours later	3 c c	25	50
	129 c c		

TABLE 2—*Free Hydrochloric Acid and Total Acidity After a Boas-Ewald Test Meal*

	Amount	Free Hydrochloric Acid	Total Acidity
15 minutes after Boas Ewald meal	20 c c	38	70
30 minutes after Boas Ewald meal	42 c c	48	78
45 minutes after Boas Ewald meal	29 c c	58	80
60 minutes after Boas Ewald meal	17 c c	60	82

Duodenal alimentation was instituted, and on the third day, the second duodenal tube was passed into the stomach. Just before the time of a duodenal feeding 30 c c of pure gastric juice were aspirated. The feeding apparatus was then attached to the duodenal tube and feeding started. At the same time suction was applied to the gastric tube. To our surprise the entrance of the first 15 to 25 c c of the milk egg mixture into the duodenum was attended by a gush of gastric secretion, so that we were immediately able to aspirate 48 c c of pure clear watery gastric secretion. The duodenal feeding and the suction on the gastric tube were simultaneously continued, with the result shown in Table 1.

Thus it is observed that 130 c c of gastric juice was secreted during the two-hour period of duodenal feeding. If a similar gastric response (as is reasonable to assume from other experiments) were to take place during each feeding, seven times that amount, or approximately 1,000 c c of gastric juice would be secreted during the twelve hours of duodenal alimentation. The figures for free hydrochloric acid and total acidity in this secretion were almost as high as those of the gastric contents after a Boas-Ewald test meal, noted by fractional examination. It was made just after the patient's admission and is appended for comparison.

CASE 4—A porter, aged 49, came to the hospital complaining of periodic attacks of heartburn and acid gaseous eructations of one year's duration. During the last two months they were more frequent. In addition he suffered from spells of nausea, headache and vertigo, also severe constipation. Physical examination was negative. Roentgen-ray examination revealed an irregularly and inconstantly deformed cap held close to the free border of the liver. Forty-five minutes after the Boas-Ewald test meal, 58 cc of gastric contents were aspirated with a free hydrochloric acid of 26 and a total acidity of 50. The results of a fractional examination after a Boas-Ewald test meal are given in Table 7.

The two tube experiment again showed a definite gastric secretion (of 172 cc) in association with the duodenal feeding.

It is interesting to note that in all of the cases cited there were moderate degrees of an irritative form of gastric disorder, which the next patient did not have.

TABLE 7—*Results of Fractional Examination After a Boas-Ewald Test Meal*

	Quantity	Free Hydrochloric Acid	Total Acidity
Immediately after taking the test meal	40 c c	44	60
15 minutes after	41 c c	42	54
30 minutes after	42 c c	46	62
45 minutes after	25 c c	36	50
1 hour after	34 c c	20	31
1½ hour after	15 c c	20	31
Total	197 c c		

TABLE 8—*Results of Two Tube Experiment*

	Quantity	Free Hydrochloric Acid	Total Acidity
Duodenal Feeding at 4 05 to 4 20			
4 05 to 4 20 obtained from stomach	60 c c	37	49
4 20 to 4 25 obtained from stomach	20 c c	44	56
4 25 to 4 30 obtained from stomach	35 c c	50	62
4 30 to 4 40 obtained from stomach	10 c c	44	56
4 40 to 5 00 obtained from stomach	17 c c	52	62
5 00 to 5 20 obtained from stomach	30 c c	54	68
Total	172 c c		

CASE 5—A waiter, aged 30, admitted on Feb 21, 1922, was highly neurotic and complained of vague symptoms of indigestion, belching of gases, sour eructations, slight pain in the left side, pain in the rectum and indefinite loss in weight. Physical and roentgen-ray examinations revealed no organic abnormalities. Forty-five minutes after a Boas-Ewald test meal only 12 cc of gastric contents could be aspirated, with free hydrochloric acid of 48 and a total acidity of 75.

Here, again, the gastric secretion responded in a similar way to both gastric and duodenal feeding—they both showed a small quantity of secretion.

Even more conclusive in this comparative respect were the findings in a case of achylia gastrica.

CASE 6—A clerk, aged 36, complained of cramplike pains in the epigastrium radiating to the left upper quadrant of the abdomen, without relation to meals, his appetite was poor, there was much discomfort after meals. Physical examination revealed no masses or tenderness, roentgen-ray examination

As shown in Table 4, 149 c c of gastric secretion during the period of duodenal feeding from 4 to 6 p m and 141 c c during the period of feeding from 6 to 8 p m. It is interesting to note that there was approximately the same type of gastric response to the same duodenal stimulation. It should be kept in mind for all these experiments that the total quantity secreted by the stomach might be even greater than the amount aspirated, because we applied suction only every half hour, and some gastric secretion probably passes through the pylorus during the interval.

That in this patient, too, the foregoing findings were not exceptional was corroborated at other times by passage of the second duodenal tube into the stomach, gastric secretion was always obtained.

TABLE 5—*Findings After Passage of Second Duodenal Tube Into the Stomach*

Date	Time of Completed Duodenal Feeding	Interval After Feeding	Quantity	Free Hydrochloric Acid	Total Acidity
July 21, 1921	1 00 p m	10 min	75 c c	58	88
	3 45 p m	15 min	50 c c	80	94
	5 40 p m	15 min	50 c c	84	100
	7 40 p m	15 min	50 c c	40	54

The outstanding characteristic of the gastric secretion in response to the duodenal feeding is that it always commences with a gush almost immediately after the milk-egg mixture touches the duodenal mucosa.

In both cases cited, gastric secretion after the Boas-Ewald test meal was plentiful, although not excessive, this seemed to tally with a similar free response of the gastric glands to duodenal feeding. Two more such cases are quoted to prove that this reaction is not the exception.

CASE 3—A woman, aged 21, an operator, came to the hospital complaining of gastric discomfort and gaseous distention after eating, which had existed for a year previous to admission. In addition, she suffered from occasional nausea and severe constipation. At times she had diffuse abdominal pains.

TABLE 6—*Results of Two Tube Experiment*

Duodenal Feeding at 3 to 3 25 p m	Quantity	Free Hydrochloric Acid	Total Acidity
Gastric aspiration during 3 to 3 25 p m	80 c c	34	50
Gastric aspiration during 3 25 to 3 40 p m	40 c c	40	52
Total	120 c c		

Physical examination revealed only tenderness over the abdominal arterial nerve plexuses. Roentgen-ray examination showed no defects in the outline of the stomach, but the cap was irregularly although inconstantly deformed. Forty-five minutes after a Boas-Ewald test meal, 22 c c gastric contents were obtained with free hydrochloric acid 44 and a total acidity of 62. The patient was placed on duodenal alimentation. The results of the two tube experiment are given in Table 6.

No secretion could be aspirated after that<sup>2</sup> until following the next duodenal feeding at 5 p m.

2 It is to be noted here as well as in repeated other tests that the mere presence of the tube in the stomach was not sufficient to stimulate gastric secretion.

periodically for about ten years from attacks which came on after shorter or longer intervals. During the upsets he would complain of pains and a gnawing or burning sensation in the epigastrium or right hypochondrium associated with gaseous eructations or regurgitations of burning acid fluids. These disturbances would come on several hours after eating and could be relieved by food or by bicarbonate of soda. He was often awakened at night because of these pains. During the attacks he lost weight. On several occasions the stools were dark. He was always tender to pressure in the epigastrium. Roentgen-ray examination in 1918 showed improper filling of the cap and periduodenal adhesions, and in 1922 there was distinct deformity of the last portion of the duodenum with fixation, also appendicular adhesions. A fractional test meal in April, 1922 (after two slices of toast and 8 ounces (250 gm) of water) showed definite hypersecretion and hyperacidity.

A total quantity of 288 cc gastric contents were obtained, as shown in Table 10. Duodenal alimentation was instituted.

TABLE 12—*Results of Later Duodenal Feeding*

12 15 stomach empty and duodenal feeding started			
	Quantity	Free Hydrochloric Acid	Total Acidity
12 15 to 12 20 aspirated from stomach	45 c c	52	68
12 20 to 1 15 aspirated from stomach	156 c c	36	54
Total	201 c c		

TABLE 13—*Results of Duodenal Feeding When Milk-Egg Mixture Was Put Into Stomach Through Tube*

9 50 to 10 00 feeding through stomach tube				
	Quantity	Free Hydrochloric Acid	Total Acidity	Description of Aspirated Fluid
10 00 to 10 10 aspirated	45 c c	40	60	( $\frac{3}{4}$ milk, $\frac{1}{4}$ whitish secretion)
10 10 to 10 20 by siphonage	99 c c	50	80	( $\frac{1}{2}$ milk, $\frac{1}{2}$ whitish secretion)
10 20 to 10 30 by siphonage	88 c c	50	80	( $\frac{3}{4}$ milk, $\frac{1}{4}$ whitish secretion)
10 30 to 10 45 aspirated	13 c c	60	100	(All milky fluid)
10 45 to 11 00 aspirated	16 c c	70	102	( $\frac{1}{2}$ milk, $\frac{1}{2}$ whitish secretion)
11 00 to 11 15 aspirated	57 c c	80	110	( $\frac{3}{4}$ milk, $\frac{1}{4}$ whitish secretion)
11 15 to 11 30 aspirated	19 c c	60	84	(No milk, all whitish secretion)
Total	317 c c			

The two tube method showed a surprisingly similar response in gastric secretion after duodenal feeding of the milk-egg mixture (April 21, 1922).

At 10 13 a. m. the stomach was aspirated, but no secretion was obtained. Duodenal feeding was started, and, just as in the former experiments, there was at once a gush of pure gastric juice.

As shown in Table 11, a total gastric secretion of 286 cc in response to 7 ounces (200 gm) of duodenal alimentation, while the same amount of gastric juice was stimulated by taking two slices of toast and a cup of tea by mouth.

That this particular cycle of secretion was not exceptional was proved at a later duodenal feeding.

During the last period (12 20 to 1 15) the end of the duodenal tube, which rested in the stomach, was allowed to hang into a bottle placed at a lower level than the patient, and the gastric juice was allowed to drain out by gravitation instead of being aspirated. It is noted that in this way only 201 cc were collected, while with frequent suction 286 cc were aspirated. Possibly the difference passed into the duodenum.

The first quantity of gastric secretion, 286 cc, stimulated by duodenal feeding, was so surprisingly profuse that it was thought interesting to compare

showed a deformed or absent cap in all the films Forty-five minutes after a Boas-Ewald test meal, only 24 c c were obtained, with no free hydrochloric acid and a total acidity of 8

The two tube experiment was carried out on May 25, 1922, three days after the Boas-Ewald test meal The first duodenal tube was swallowed on May 24, about 9 p m The next morning the tube was in the duodenum, and duodenal feedings were given at 10 a m, 12 and 2 p m Just before the 4 o'clock feeding the second tube was passed into the stomach, and suction yielded no secretion Duodenal feeding was given from 4 to 4 25 Aspiration during

TABLE 9—*Results of Two Tube Experiment*

	Total Amount	Free Hydrochloric Acid	Total Acidity
Aspiration at 8 a m, just before feeding, showed	8 c c	0	22
Duodenal feeding 8 to 8 30			
Aspiration at 8 45	12 c c	0	42
Aspiration at 9 15	7 c c	16	74
Aspiration at 9 30	4 c c	36	75
Aspiration at 9 50	10 c c	46	66
Total	33 c c		

TABLE 10—*Results of Fractional Test Meal*

	Total Quantity	Free Hydrochloric Acid	Total Acidity
10 minutes after Boas Ewald meal	30 c c	14	24
20 minutes after Boas Ewald meal	34 c c	19	28
30 minutes after Boas Ewald meal	44 c c	50	68
40 minutes after Boas Ewald meal	51 c c	56	74
55 minutes after Boas Ewald meal	35 c c	80	94
1 hour after Boas Ewald meal	38 c c	50	62
1 hour 15 minutes after Boas Ewald meal	20 c c	40	50
1 hour 45 minutes after Boas Ewald meal	36 c c	54	66
Total	288 c c		

TABLE 11—*Gastric Juice After Duodenal Feeding*

	Quantity	Free Hydrochloric Acid	Total Acidity
10 13 to 10 15 (first 2 minutes)	48 c c	36	50
10 15 to 10 25 (first 10 minutes)	50 c c	76	88
10 25 to 10 35	50 c c	56	70
10 35 to 10 45	30 c c	46	58
10 45 to 11 00	50 c c	48	68
11 00 to 11 15	38 c c	54	68
11 15 to 11 30	15 c c	60	70
11 30 to 11 45	5 c c	4	20
Total	286 c c		

this whole time and for one hour after the feeding was stopped could bring forth absolutely no gastric juice in spite of continuous and drastic suction with the patient in various upright and reclining postures

Most interesting and instructive were the experiments in a chronic ulcer patient with marked alimentary hypersecretion and hyperacidity (Later the patient was operated on by Dr Willy Meyer, and the condition proved to be a gastric ulcer )

CASE 7—The patient had been at the hospital on two occasions, the first time in January, 1918, and the last time in April, 1922 He had been suffering

# DIGITALIS ELIMINATION <sup>1</sup>

HARRY GOLD, M D

NEW YORK

The fate of the digitalis bodies in the animal organism is one of the most interesting, though perplexing, problems in the study of this group of drugs. The more basic questions of digitalis action that inevitably arise in a consideration of such phenomena as tolerance, cumulation, difference in persistence, actions and effects, are imperfectly understood. A large literature has accumulated, still our knowledge is fragmentary, the evidence often contradictory, having been obtained under a variety of experimental conditions in different animals with different digitalis bodies.

Efforts to recover the digitalis bodies from hearts poisoned by them have been quite consistently negative <sup>1</sup>. While they cannot be recovered from living heart muscle brought to a standstill, they can be recovered from incubations of the drug with emulsions of the heart muscle <sup>2</sup>. The recovery of the largest part of the drug from the supernatant fluid of these incubations would contradict the observation that heart muscle contains a substance with a specific affinity for these glucosides <sup>3</sup>. There seems to be no evidence that these drugs are absorbed by the heart to any greater extent than by other tissues <sup>4</sup>. There is abundant evidence, however, both clinical and experimental, <sup>5</sup> that the heart is more susceptible to these drugs than other tissues. Perfusion experiments have shown that minute reduction in the concentration of the perfusion fluid occurs in passage through hearts <sup>6</sup>. Whether these quantities are fixed or destroyed by the heart is unknown.

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\*From the Department of Pharmacology of Cornell University Medical College

1 Cloetta, M., and Fischer, H. F. Ueber das Verhalten des Digitalins im Organismus, *Arch f exper Path u Pharmakol* **54** 294, 1906. Straub, W. Quantitative Untersuchung des Eindringens von Alkaloiden in Lebende Zellen, *Arch f d ges Physiol* **98** 233, 1903. Hatcher, R. A. The Absorption, Excretion, and Destruction of Strophanthin, *Am J Physiol* **23** 303, 1908. Clark, A. J. The Factors Determining Tolerance of Glucosides of the Digitalis Series, *J Pharmacol & Exper Therap* **4** 399, 1912.

2 Cloetta and Fischer, and A. J. Clark. Footnote 1.

3 Schliomensun, B. Ueber die Bindungsverhältnisse zwischen Herzmuskel und Digitalis, *Arch f exper Path u Pharmakol* **63** 294, 1910.

4 Hatcher, R. A. Footnote 1. Clark, A. J. Footnote 1.

5 Fraser, T. R., and Mackenzie, A. T. *Strophanthus Saimentosus*, Its Pharmacologic Action and Its Use as an Arrow Poison, *Trans Roy Soc, Edinb* **47** 341, 1910.

6 Clark, A. J. The Influence of Ions upon the Action of Digitalis, *Proc Roy Soc Med Therap & Pharm Sect* **5** 181, 1912. Straub, W. Quantitative Untersuchungen über den Chemismus der Strophanthinwirkung, *Biochem Ztschr* **28** 392, 1910.

how much gastric secretion would be stimulated when the milk-egg mixture was put directly into the stomach through the tube rather than into the duodenum

A total of 317 c c gastric contents were obtained, as shown in Table 13. This figure might have been a little higher because some of the gastric contents were evacuated into the duodenum. But, taking even this factor into consideration, the 317 c c represented less gastric secretion than was obtained after the duodenal feeding, because the 317 c c included approximately 220 c c. of the original milk-egg mixture.

#### CONCLUSIONS

It is evident that one cannot put the stomach at rest from secretion by duodenal alimentation alone. None of my patients used alkalis by mouth or any other medication during the experiments. There seems to be a definite cycle of gastric secretion which starts just as soon as food enters the duodenum, and which depends on the type of patient we are dealing with. The greater the response of the secretory mechanism of the stomach to food intake by mouth, as in cases with hypersecretion, the greater also will be the gastric response to duodenal alimentation, the less the gastric response to food in the stomach as in some cases of achylia, the less gastric secretion in response to duodenal alimentation.<sup>3</sup> There are several factors which have been found to influence this reaction of the stomach to duodenal feeding, but they will be taken up in another paper. The exact physiologic mechanism whereby this reflex is brought about is still to be determined.

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3 It is interesting to make a comparison with the findings of Dr McClure. He noted that the enzyme concentration of the pancreatic secretion in response to various types of foods was the same, no matter whether the feeding was into the stomach or duodenum. (Paper read at the meeting of the American Gastro-Enterological Association.)

preparation was determined at intervals of three hours, one day, two days, three days, four days, and then at intervals of four days as long as persistence was exhibited

*Protocol of a Typical Experiment*—4/4/23 Cat Male, weight, 2.66 kg Phenol for local anesthesia 10 43, injected 75 per cent cat unit per kg by vein (3.99 c.c. total) 10 45, licks repeatedly 10 57, emesis

4/6/23 Animal slightly depressed Weight, 2.48 kg 11 15, began injection of ouabain solution 1 250,000 12 00, convulsion, death

Time 45 minutes Total 25.5 c.c. injected

*Calculation of Elimination*—The matter of calculation presented some difficulties. First, as the cat unit is based on the average of several experiments, that 75 per cent of the calculated fatal dose should be fatal to some was inevitable. Second, as the standard cat unit had been established on animals under the ordinary conditions of feeding and in the average state of nutrition, one could not say whether the cat unit of 0.1 mg ouabain would apply to animals that had been starved several days (toxic doses of digitalis producing such marked and prolonged digestive upset that the animal would for days eat little or nothing and lose considerable weight). Third, the calculation would show considerable difference depending on whether the original or the new weight on the day of the ouabain injection was used.

We cannot be absolutely certain that the method is correct in all details, in fact, we are aware of unavoidable flaws. Nevertheless, we feel quite certain of the general principles, the validity of which is supported in part by facts, in part by rational assumptions. That the cat unit based on the average of several experiments is a constant, has been repeatedly demonstrated. Therefore, the animals in which 75 to 80 per cent of a cat unit was fatal, were considered more susceptible than the average, the remaining animals more tolerant than the average. The cat unit was then readjusted for either the remaining animals of that series, or, as in one case, for the remaining animals used with that preparation. Deaths after the first day were entirely omitted from the calculation.

Second, to determine whether starvation altered the fatal dose, a number of animals were starved over a certain period of time, after which they were killed by the slow intravenous injection of ouabain solution 1 250,000. The results are given in Table 6. From the quantity of ouabain necessary to kill after starvation, the fatal dose per kilogram was determined on the basis of the original, the new and the mean of the two weights. It is evident, from the data, that the old weight brings the fatal dose as far below the cat unit as the new weight brings it above, and that the fatal dose equals the standard cat unit of 0.1 mg ouabain if the mean of the original and the new weights is taken.

Incidentally, we might note that the fatal dose rises for a time at least with the period of starvation and the percentage of weight lost. It is also rather interesting that on the basis of the original weight, Animal 3 is more susceptible than Animal 4, on the basis of the new weight, their susceptibility is reversed, corresponding to the greater loss of weight in Animal 3. A similar tendency to a greater rise in the fatal dose corresponding to the greater loss in body weight is also seen in Animals 1 and 2. This phenomenon is probably due to the loss of gastro-intestinal contents, fluid and other body substance that normally take up no drug, but affect in lowering the fatal dose per kilogram by their weight.

To calculate the percentage of elimination, the amount of ouabain actually required to kill after the interval following the initial injection is subtracted from the amount theoretically, required to kill an animal weighing the average of the original and the new weights, the result representing the amount of digitalis in the body. The latter subtracted from the amount given in the



The largest part of ouabain or digitoxin is eliminated from the blood stream in a few minutes<sup>7</sup> There is evidence that their disappearance from the body is determined in part by destruction, in part by elimination through the bile<sup>8</sup> and the urine<sup>9</sup>

Studies concerned with the estimation of the drug in the heart, in the remaining tissues and in the excreta have yielded in the main only qualitative information The problem has been approached from another standpoint, namely, elimination has been determined in terms of persistence of action By such a study, Hatcher,<sup>10</sup> though not attempting to establish the precise curve, about ten years ago, was able to show that the so-called cumulative action of digitalis was dependent on the persistence of action of previous doses, and that the persistence of some digitalins was considerably longer than that of others He considered his results as affording a starting point for a reinvestigation of the subject of persistence and cumulation Certain important questions remained unanswered, namely, (1) whether different specimens of digitalis are eliminated at the same rate, and (2) the nature of the line or curve of elimination No subsequent work, either clinical or experimental, has investigated these problems This paper is concerned with a report of the results obtained in a study of the rate of digitalis elimination in terms of persistence of action

#### METHOD

Over 200 experiments were performed on the cat with the following preparations three tinctures of digitalis, one specimen of digitoxin, one preparation of digitalis, made a year previously, consisting of the fraction left after ether extraction, and one commercial specimen that had been found to be rapidly eliminated The activity of each preparation was first determined in the usual manner in terms of the cat unit<sup>11</sup> With few exceptions, 75 per cent of a cat unit per kilogram of body weight was injected by vein Freshly prepared ouabain solution 1:250,000 was then injected slowly into the vein at different intervals following the initial dose The persistence of action in the case of each

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7 Hatcher, R A The Elimination of the Digitalis Bodies, *J A M A* **61** 386 (Aug 9) 1913

8 Hatcher, R A, and Eggleston, C Studies in the Elimination of Certain of the Digitalis Bodies from the Animal Organism, *J Pharmacol & Exper Therap* **12** 405 (March) 1909 Hatcher, R A Footnote 1

9 Cloetta and Fischer Footnote 1 Hatcher and Eggleston Footnotes 1 and 8

10 Hatcher, R A The Persistence of Action of the Digitalins, *Arch Int Med* **10** 268 (Sept) 1912

11 Hatcher, R A, and Brody, J G Biological Standardization of Drugs, *Am J Pharm* **82** 360, 1910

## COMMENT

An examination of the data presented in Tables 1 to 5 will undoubtedly raise the question whether any information as to the general behavior of digitalis persistence can be obtained in view of such marked,

TABLE 3—*Percentage of Elimination* \*

Interval in Days	3 Hours	1	2	3	4	8
	35.2	50.0	100.0	92.0	72.9	100.0
	26.0	53.1	100.0	82.8	72.6	100.0
	57.9	71.0	100.0	61.8	53.8	85.7
	77.1	24.6	100.0	53.4		
	11.3	100.0	100.0	71.2		
			95.3			
			85.7			
			51.8			
			50.0			
Averages	41.9	59.7	86.9	72.4	66.4	95.0

\* The specimen used was tincture digitalis prepared from a German leaf. The activity was 77.6 mg per cat unit. With this specimen about 8 per cent of the animals (two out of thirty six) died a few minutes after the initial injection. The cat unit was readjusted for the individual groups wherever necessary (see method of calculation). About 13 per cent (five out of thirty six) of the animals died from two to six days after the initial injection. In some of the latter, the symptoms following the initial dose betrayed susceptibility greater than the average, in others, no such susceptibility was discerned.

TABLE 4—*Percentage of Elimination* †

Interval in Days	3 Hours	1	2	3	4	8
	25.0	81.8	65.5	79.7	100.0	
	28.3	82.2	65.6	70.4	92.7	
	44.8	83.9	66.5	64.6	82.6	
	55.2	83.6	58.1	44.5		
		100.0	100.0	29.9		
		67.5	26.3	100.0		
		49.4				
		24.0				
		12.4				
Averages	38.3	78.2	63.6	64.8	91.7	

† The specimen used was a fraction obtained after ether extraction made about a year previously from a specimen of digitoxin Keller. The activity was 0.255 cc per cat unit. With this specimen, only one animal died in a few minutes after the initial dose. About 6 per cent (two out of thirty one) died from one to four days after the initial injection. The three animals of the four-day series showed slight depression with the first injection. A dose of 100 per cent of the fatal was then given to another animal (G). On the following day, it showed considerable depression, it died four days after the injection. Animal G of the three-day series showed peculiar tremors involving the entire body when it was put on the board on the second day after the initial injection. These nervous symptoms persisted for several hours. On the following day, it took over 100 per cent of the theoretic fatal dose of ouabain to kill.

TABLE 5—*Percentage of the Fatal Dose Necessary to Cause Death*

Interval in Days	1	2	3	4
	77.8	89.4	46.3	96.2
	94.9	51.0	54.3	84.8
	92.8	59.5	59.5	75.2
	76.8	57.1	87.5	
	51.0	39.5	96.9	
	35.2			
Averages	71.0	58.5	68.8	84.5

Digitoxin Merck

apparent individual variations. It was common experience in Hatcher's<sup>10</sup> study, as also in the present one, to find that one animal would eliminate apparently more in one day than another would in two or three days after receiving a similar dose of the same preparation.

original injection (the ouabain equivalent of 75 per cent cat unit of digitalis) gives the quantity eliminated, which, in turn, divided by the amount given in the initial dose yields the percentage of elimination

*Example of a Complete Calculation*—The quantities are all expressed in terms of ouabain. Sixty animals used with preparation—their average theoretic cat unit, 0.1 mg, 23 animals died with 75 to 80 per cent of theoretic fatal dose—their average cat unit, 0.0769 mg, 37 animals remaining—their average cat unit, 0.114 mg

Cat 1, original weight, 3.44 kg, new weight, 3 kg, mean weight, 3.22 kg. Amount required theoretically to kill = 0.326 mg ( $3.22 \text{ kg} \times 0.114$ ). Amount required actually to kill after twenty-four hours = 0.181 mg. Therefore, amount in body after twenty-four hours = 0.145 mg ( $0.326 - 0.181$ ). Amount given in

TABLE 1—Percentage of Elimination\*

Interval in Days	3 Hours	1	2	3	4	8	16	22
	15.1	15.6	37.6	18.7	1.3	37.0	49.2	40.0
	19.4	24.6	40.2	26.0	35.0	49.5	64.3	70.8
	22.6	29.0	50.0	30.6	52.8	67.0	68.2	86.5
	100.0	31.3	53.3	31.2	53.5	100.0	100.0	100.0
		57.5	60.0	42.7	68.8			
			60.8	70.0				
Averages	19.0	31.6	50.3	36.5	62.4	63.4	70.4	74.3

\* The specimen used was tincture digitalis prepared from German leaf. The activity was 68 mg per cat unit. The following were omitted from the final averages: Animal 4 of the three hour series; Animal 1 of the four day series. About 38 per cent of the animals with this preparation died a few minutes after the initial injection, the remaining ones became 15 per cent tolerant (see method of calculation). It is possible that this procedure prolongs the curve of elimination somewhat beyond the actual limit. Of the animals that did not die a few minutes after the initial dose, 26 per cent died from two to twelve days later, some showing evidence of infection, many showing no such evidence.

TABLE 2—Percentage of Elimination\*

Interval in Days	3 Hours	1	2	3	4	8
	45.5	60.0	51.7	62.4	100.0	
	57.5	64.7	42.4	44.0	97.4	
	12.8	78.9	48.2	99.9	79.4	
	100.0	48.7	79.0			
		25.0	57.5			
		13.5	53.9			
			92.3			
Averages	54.0	55.46	50.8	67.1	92.9	

\* The specimen used was tincture digitalis made from a commercial leaf (source not determined). The activity was 140 mg per cat unit. The following were omitted from the final averages: Animal 6 of the one day series; Animals 4 and 7 of the two day series. With this specimen, about 25 per cent of the animals (eight out of thirty-one) died in a few minutes after the initial injection. The cat unit was readjusted for the remaining animals of each series wherever necessary (see method of calculation). No animals with this specimen died after the first day from the initial dose.

original dose = 0.258 mg (75 per cent cat unit per kg) 0.258 mg — 0.145 mg = 0.113 mg, quantity in body after twenty-four hours 0.113 — 0.258 = 42.1 per cent elimination in twenty-four hours

The results, then, are expressed as percentage of elimination of the dose injected, the final figure for each interval representing the average of three to nine experiments. It will be seen that certain experiments are omitted from the final results because of apparent tolerance or susceptibility out of all proportion to that of the remaining members of the series, in other cases, because of the atypical behavior of the animal. On the other hand, some irregular results were not omitted from the final because by their inclusion the average did not depart to any considerable extent from the percentage of elimination of the majority and more consistent animals.

dose, we assume. We are still aware that the animal might conceivably have been tolerant also to the extent of a considerable portion of the initial dose and, therefore, may have really eliminated little or nothing. It does not seem probable. It appears likely that the converse of this reasoning applies to those cases in which the sum of the initial and final dose after the interval is less than the average fatal dose<sup>10</sup>. The fact, together with the assumption, therefore, would indicate that tolerance to the digitalis bodies is in part, at least, measured by the capacity for elimination. They confirm the observation of Hatcher<sup>10</sup> that different species of animals—the cat, the dog and the rabbit—are tolerant to digitoxin in proportion to their capacity to eliminate it. However, one is led to suspect that this is not always true from the occasional occurrence of a rather severe reaction from the initial dose in an animal which after the interval showed greater elimination than the other members of the series that were less effected by the initial injection.

#### PERSISTENCE OF ACTION VERSUS ELIMINATION

The terms "elimination" and "persistence of action" have been used interchangeably. The results have been expressed as percentage of elimination of the dose injected. Lest the word "elimination" obscure the true nature of the determination, let us again state that the results express elimination of activity and not of the drug. Although ouabain and digitoxin apparently produce similar effects, those of the former disappear rapidly while those of the latter disappear slowly. Hatcher<sup>10</sup> suggested that this shows a difference in capacity for eliminating the two drugs. Eggleston,<sup>13</sup> on the basis of a clinical investigation, expressed a similar opinion for the same reason, deducing further that the persistence of digitalis expresses, not the "lasting effects of any injury to the heart," but the "actual presence of the drug in the tissues." This conception led the latter to the view, expressed also by an earlier investigator,<sup>14</sup> that the phenomenon of so-called cumulation represents simple storage of small fractions of previous doses fixed in the tissues.

These deductions make inevitable the conclusion that the curve of elimination of the drug and of its persistence of action should coincide. The diagrams show, with digitoxin, also rather consistently with tinctures of digitalis, a tendency to greater elimination after one day than after two or three days. That an animal could eliminate more drug in the first day than in the first two or three days is quite inconceivable, of course. That the drug might diffuse rapidly into the tissues, to be subsequently returned to the circulation and exhibit thereby a greater

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13. Eggleston, C. Clinical Observations on the Duration of Digitalis Action, *J A M A* **59** 1352 (Oct 12) 1912.

14. Van der Heide, W. Ueber die Kummulative Wirkung des Digitalins und Helleboreins, *Arch f exper Path u Pharmacol* **19** 127, 1885.

Though individual variations are an attribute of any biologic work, we were not altogether unconcerned about this question until results were examined more carefully in the light of fuller data. Care has been taken to refer to these variations, in part at least, as apparent. It must be remembered that the calculations have been made on the basis that susceptibility is the same for each animal. Therefore the data seem to indicate that individual differences are solely those of elimination. The cat unit of the animal in which elimination is being determined is, of course, an unknown factor. That the cat unit of individuals vary is certain, that the average of several experiments is generally a constant is equally certain. So far, then, as variations in the final results are dependent on susceptibility, the averages approach a constant. It is quite probable that both factors, elimination and susceptibility, account for the individual differences. At all events, after making allowance for occasional variations that disturb the results of a series, it is evident that the behavior of the majority and more consistent animals

TABLE 6—*Effect of Starvation on Fatal Dose*

Animal	Weight Lost, Per Cent	Starvation Time	Fatal Dose on Bases of Weight		
			Old	New	Mean
1	14.5	6 days	0.0941	0.1100	0.1016
2	17.8	6 days	0.0774	0.0941	0.0849
3	35.8	10 days	0.0837	0.1305	0.1020
4	21.9	10 days	0.0945	0.1210	0.1041

approaches rather closely the average elimination obtained for the various intervals.

The relation of susceptibility to elimination has a bearing on this question. Many observations have been made which show that difference in tolerance of different species to strophanthin expresses a degree of tissue immunity.<sup>12</sup> Considerably greater quantities of the drug are necessary to affect the hearts of species known to be tolerant than of those known to be susceptible. Clark<sup>1</sup> says that tolerance to strophanthin offers an interesting contrast to that of atropin, with the latter drug, tissue immunity does not obtain, tolerance being determined by the capacity for absorption and destruction by the liver. Tissue immunity does not, however, seem to be the only explanation of differences in susceptibility of individuals of a species. After a short interval following the initial injection of 75 per cent of the fatal dose, an occasional animal would take 20 per cent or more above the full theoretic fatal dose of ouabain. That this animal is more tolerant than the average, we know. That it has eliminated practically all of the original

<sup>12</sup> Evans, C. L. Toxikologische Untersuchungen an bioelektrischen Strömen, Ztschr. f. Biol. **59** 397, 1912. Clark, A. J. Footnote 1.

The procedure with digitoxin differed somewhat from that with the other preparations (Table 5). We were interested mainly in the phenomenon of rising toxicity with digitalis, which, there was reason to suspect might be due to digitoxin. As it is rather difficult to establish the exact fatal dose of digitoxin, a toxic dose—0.2 mg per kilogram—

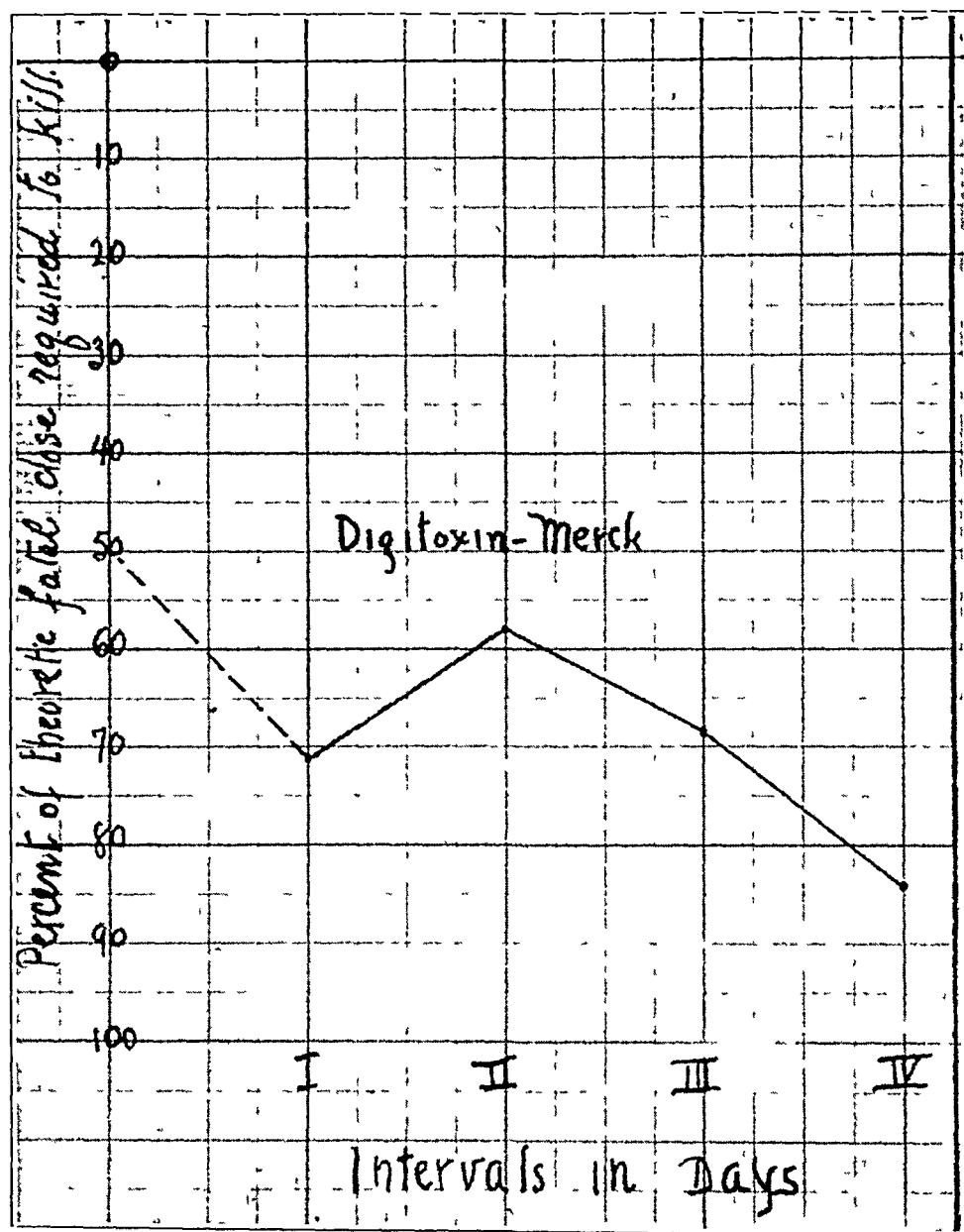


Diagram 2—Curve of persistence of action for the specimen of digitoxin (Table 5)

was injected by vein. After the intervals, the injections were completed with ouabain solution and the results expressed as percentage of the fatal dose required to kill. One therefore does not know how much, if any, of the digitoxin was eliminated during the first day. After twenty-four hours, the animals took an average of about 70 per cent of the

action on the second or third day than on the first, is a possibility. That a certain dose producing a given action might simply exhibit a greater effect on the second or third day than on the first seems less abstruse. However this may be, also irrespective of the nature of digitalis action, whether by chemical union with heart tissue in a quantity or manner not discernable by ordinary extraction, or by alteration of the physical state of the cells without such union,<sup>15</sup> it appears that the curves of effects and elimination of the drug from its seat of action do not run strictly parallel, it appears probable, therefore, that digitalis can produce an effect that persists independently to a degree, at least, of the presence of the drug.

This rise in toxicity did not occur with the commercial preparation that was practically completely eliminated in from three to four hours.

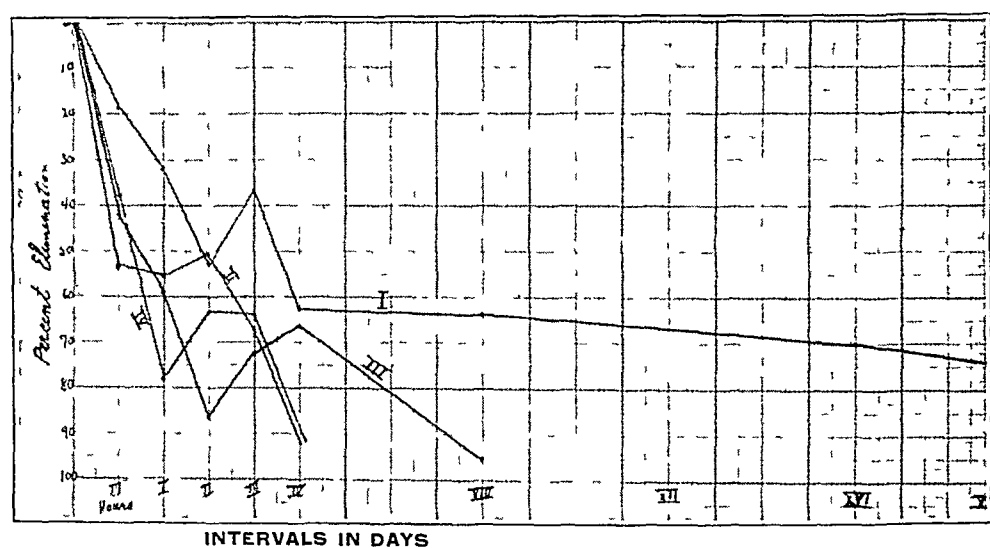


Diagram 1—Curves of elimination for the preparations of digitalis employed. The numbers on the curves refer to the corresponding Tables 1 to 4.

Also after an interval of two days, six animals failed to show any evidence of persistence of action of the drug. The rise in activity occurred with our specimen of digitoxin, which showed considerable persistence after the same length of time. On the basis of the assumption that the capacity for eliminating the different digitalis bodies is not the same, we must conceive that the effect is not entirely independent of the presence of the drug. One might say, therefore, that a dose of a digitalis body produces an effect that increases with the persistence of the drug at its seat of action, this phenomenon gives rise to the increasing intensity of effect (Charts 1 and 2) when little or none of the drug has been eliminated, and prolongs the curve of elimination when the drug begins to disappear.

method The three repeated doses produced effects that could not be entirely accounted for by simple addition The apparent contradiction of the two results points to a potentiation of effects of repeated doses of digitoxin, so that while recovery in many animals, to a large degree, may occur in four days after the single dose, the effects of repeated doses are not so rapidly recovered from

The nervous phenomena noted in this animal have not been frequently referred to, although an action on the central nervous system by the digitalis bodies is recognized The white rat is known to exhibit nervous symptoms with digitoxin resembling strychnin poisoning<sup>10</sup> Nervous symptoms were observed to some degree in animals receiving a single dose of digitoxin, but little attention was paid because they seemed much like the temporary depression associated with nausea With repeated injections, however, as noted above, the incoordination and general weakness were considerably more pronounced and seemed to obtain while the animal lapped milk and appeared playful Potentiation may in part explain so-called cumulation in the effect of digitoxin on the heart as well as on the central nervous system

One specimen of tincture of digitalis (Table 3) showed slight persistence after two days This was confirmed by the repeated daily injection into the vein of 50 per cent of a fatal dose into two animals One animal (*C*) died about four hours after the fourth dose, the second animal (*D*) died about five minutes after the fifth dose This elimination is rather striking compared with digitoxin persistence, in which case the third dose at intervals of four days was fatal

If an animal could recover from the effects of a smaller dose more rapidly than from those of a larger one of the digitalis bodies, its behavior would be similar to that toward many other drugs Two animals received daily injections by vein of 25 per cent of the fatal dose of the tincture (same specimen as used in Table 3) One (*E*) died several hours after the eleventh dose, the other (*F*) died several hours after the tenth dose These results do not show that small repeated doses are more rapidly eliminated than larger ones given in the same way On the contrary, they point to the conclusion that the longer small doses are repeated the relatively greater persistence they show, confirming the possibility observed with digitoxin that repeated doses sensitize the heart to subsequent administration to a degree not observed after a single large dose

Chart 1 represents the curves of elimination for the preparations of digitalis employed in this study Dooley,<sup>17</sup> working in this labora-

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17 Dooley, M S Evidence for the Presence in Digitalis of a Principle that is Eliminated Rapidly After Intravenous Injection into the Cat, *J Pharmacol & Exper Therap* **17** 277, 1921



fatal dose of ouabain to kill. If none was eliminated, our initial dose of 0.2 mg. was only about 30 per cent of the fatal dose. But since 0.3 mg. was almost fatal to two animals, it seems safe to assume that about 0.4 mg. was the fatal dose of our specimen of digitoxin. It seems probable, therefore, that there is at first a somewhat rapid descent of action, to show which we do not have the necessary data. It is indicated in Chart 2 by the broken line. This determination was not made because of the difficulty, as stated, of obtaining the exact fatal dose of digitoxin, also because our purpose was well served without it. It is plain that a given dose of digitoxin produces a greater effect on the second than it does on the first day.

The curve (Chart 2) does not show complete elimination after four days, yet the apparently slight persistence of digitoxin action after that interval seemed rather striking against the accepted notion about this digitalis body. Digitoxin has been considered one of the most persistent of the digitalis principles. That pure digitoxin crystals are not easily prepared is seen from Schmiedeberg's description,<sup>16</sup> in which he states also that he was able to obtain only from 2 to 2.5 gm. of the pure crystals from 20 kg. of the leaf. Although Schmiedeberg has shown that Nativelle's crystalline digitalin was a mixture consisting mainly of digitoxin, the name of this mixture is used as a synonym for digitoxin. While Merck's crystalline digitoxin is considered of most constant activity, it is apparent that one cannot be absolutely certain that the product employed is pure, and therefore one cannot be certain the behavior of any two preparations will be exactly alike.

The apparently rapid disappearance of digitoxin action was tested by the injection of the same dose, 0.2 mg. per kilogram by vein, repeated every four days. One animal (*A*) died thirty minutes after the third injection, having vomited after the first two, but not following the third dose. It took altogether 0.6 mg. per kilogram in a total period of eight days. A second animal (*B*) behaved similarly after the first two doses. Two minutes after the third injection, saliva began to drool, but there was no emesis. It began to show peculiar nervous symptoms, the entire body was limp, there was marked incoordination, the animal occasionally jumping with the hind legs together like a rabbit, there was a side to side movement of the head, it lapped milk, its expression seemed playful. These symptoms improved on the following day, but depression set in, the heart became very slow and irregular, it died four days after the last injection.

It is difficult to reconcile the facts shown by these two experiments with the apparently slight persistence shown by the combined ouabain

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<sup>16</sup> Schmiedeberg, O. Untersuchungen über die pharmakologisch wirksamen Bestandtheile der *Digitalis purpurea* L., Arch. f. exper. Path. u. Pharmacol. 3 16, 1875.

a cat On the following day, it showed extreme depression, and only 8 per cent of a fatal dose of ouabain caused death These facts support the data given in Table 5 that the effects of a fairly large dose of digitoxin that does not kill immediately may show a progressive increase It has already been indicated, also, that from the standpoint of elimination these two fractions stand at opposite extremes That neither substance is pure appears quite certain That they exist in the leaf in the form in which they are extracted is considerably less certain All one can say is that digitalis yields, in variable amounts, these two substances which show to a variable degree these entirely different tendencies one develops its full action in a few minutes and shows almost no persistence after a short time, the other is capable of showing a progressively increasing effect and almost complete persistence after a similar length of time The resultant of these forces, one rising, the other falling, is exhibited in the more complex and variable curve of digitalis elimination

Throughout the work our attention has been called to the not infrequent occurrence of delayed death following large doses of the digitalis bodies The failure to include deaths after the first day in the calculations is not intended to imply that such deaths may not in a number of cases have been due directly to the action of the drug Let us recall here a few observations relating to this question The rise in intensity of digitoxin action has already been referred to, also, the occurrence of death as long as four days after the administration had been stopped (Animal *B*) The rise in intensity of action appeared to be more marked with repeated small injections than with a single large one (Animals *E* and *F*), it resulted in death when the dose approached, presumably, rather closely the fatal amount (Animals *C*, *E*, *F* and *G*) The last doses were frequently not followed by emesis The largest number of delayed deaths occurred with that preparation that showed the closest digitoxin-like behavior (Table 1) There were no late deaths with the preparation that showed the least digitoxin-like action (Table 2)

It is of some interest to consider the part played by the digitoxin-like fraction of digitalis in the cases of late death following the administration of large doses of the drug It is of greater importance to consider the possible clinical bearing of the facts presented above It is undoubtedly true that, with proper usage, deaths from digitalis are exceedingly uncommon Considerably less common are deaths following digitalis administration in which definite causal relation has been established by the electrocardiogram The occurrence of death soon after the administration of the drug in a patient whose previous condition gave no reason to suspect impending death is generally taken as the essential evidence when a causal relation is suspected But it is

tory, found evidence for the presence of a rapidly eliminated fraction in the tincture of digitalis from the observation that more was required by slow than by rapid injection to cause death. Weiss and Hatcher<sup>18</sup> subsequently described the isolation of this fraction. In another way, then, the presence in the tincture of digitalis of a rapidly eliminated fraction is confirmed. The general behavior of this fraction is also confirmed, individuals vary in their capacity to eliminate it, its quantity varies with different preparations. In one preparation, 20 per cent of the original dose was eliminated in from three to four hours, in three others, as much as 40 to 50 per cent of the activity of the initial dose was eliminated in the same length of time.

The curves were not continued to obtain 100 per cent elimination. While there is abundant evidence that small fractions of action or effect persist beyond the limits indicated, the method is not sufficiently exact to determine them. The general principles, nevertheless, stand out clearly. As for a single preparation, after a large intravenous dose there is rapid elimination at first, a secondary rise in toxicity, followed by a more gradual decline of action. The persistence at the end of twenty-four hours is no index of the behavior of the preparation over longer periods of time. At the end of one day, the persistence of two preparations may be practically the same, at the end of two days, about 50 per cent of one of these may be eliminated, while about 85 per cent of the other may be eliminated. Again, at the end of two days, the persistence of two preparations may be practically the same, while at the end of four days about 40 per cent of one may be eliminated and about 90 per cent of the other. It is evident, therefore, that the curve of digitalis persistence is not a simple one, that it varies with different tinctures, and that the ultimate persistence of action of one tincture may be several times longer than that of other tinctures.

The specimen of the fraction obtained after ether extraction behaved in a manner similar to that of the ordinary tincture (Table 5).

The meaning of this peculiar curve of digitalis elimination and its variations with the different tinctures find an explanation in facts relating to digitoxin and the rapidly eliminated fraction. A dose of the latter that will kill in a few minutes is generally about the fatal dose or slightly more. The dose of digitoxin that kills in a few minutes is considerably larger than the fatal dose<sup>10</sup>. Much smaller doses will be fatal after the lapse of a day or after a longer time. Thus, 0.8 mg per kilogram by vein was the dose of our specimen of digitoxin that killed at once. A dose of 0.3 mg per kilogram by vein was given to

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<sup>18</sup> Weiss, S, and Hatcher, R. A. Study of a Digitalis Body Which is Eliminated Rapidly After Its Intravenous Injection in the Cat, *J Am Pharm A* 12 26, 1923.

to maintain optimum improvement over weeks and months. It is obvious that one cannot say whether absorption or elimination accounts for the fact that one preparation required two and a half times the dose of the other in point of activity to maintain digitalization.

An interesting light is thrown on the subject by the extreme variations in the reports of the persistence of various digitalis phenomena. Eggleston<sup>23</sup> reports heart block lasting from three to six days. Bastedo<sup>23</sup> reports heart block lasting three and one-half weeks. Kay<sup>24</sup> found that the slowing in auricular fibrillation persisted from three to five days after administration of the drug by the high dose method. Robinson<sup>25</sup> found this slowing to last from four to fifteen days, with an average of nine days. These clinical data seem strikingly in accord with evidence given in Chart 1. We are aware of the numerous factors that might conspire to produce these variations—the nature of the heart condition, the end point for observation, the total dosage, etc. These facts, nevertheless, in the light of observations recorded in this study, make it difficult to escape the conclusion that the problem of digitalis persistence in man cannot be disposed of with one preparation. That departures from an average, so determined, represent merely individual variations of susceptibility, and elimination fails to take cognizance of a simple but fundamental fact—in behavior and composition, different specimens of digitalis vary. That this fact applies not only to activity and absorption, but also to elimination, experimental evidence shows and clinical observation seems to confirm. We should state here that one does not escape the difficulty by employing a preparation always made by the same manufacturer. Though the activity may be the same, different lots of the tincture being prepared from different lots of the crude drug will in all probability vary in their rates of elimination.

The application, without evidence, of results obtained with one species to another is indeed a fruitful source of confusion in the study of digitalis. Pardee<sup>22</sup> states "It is evident that the animal experiment would not give a definite answer to the question of the rate of disappearance of the drug, because of the marked variations that were found between different species." But as marked as are the variations between certain species, as striking seems to be the similarity in the behavior, in some respects, of the cat to man toward some of the digi-

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23 Bastedo, W. A. The Signs of Overdosage in Digitalis Administration, *Am. Practitioner* **46** 609, 1912.

24 Kay, W. E. The Rapid Administration of Digitalis in Cardiac Decompensation, *California State J. M.* **17** 329, 1919.

25 Robinson, G. C. The Rapidity and Persistence of the Action of Digitalis on Hearts Showing Auricular Fibrillation, *Am. J. M. Sc.* **159** 121, 1920.

not rare to find cases with this clinical history (two such have recently been seen by the writer) After more or less continuous administration of digitalis for months or years with occasional emesis from overdigitalization, there are suddenly toxic signs in the form of disordered rhythm—frequent extrasystoles, coupling, etc.—whereupon the drug is discontinued There is no vomiting at this time The general condition may or may not seem worse The patient dies suddenly, days after the last dose of the drug In view of the fact that sudden death may occur in patients suffering from chronic cardiac disease, attributed generally to embolism or coronary thrombosis—in some cases observed postmortem, in other cases surmised—one can say nothing positively about the rôle played by digitalis The facts stated above, however, suggest a possibility that deserves more careful investigation

#### THE CLINICAL PROBLEM

The need for standards in digitalis therapy has been felt particularly by those clinicians who have had large numbers of patients with cardiac disease under their care A long stride was made by the advent of the cat unit determination of activity<sup>11</sup> and the application of this unit to digitalis dosage in man<sup>19</sup> Expressed in terms of activity, much confusion in digitalis dosage has been reduced to relative order While it is commonly recognized that activity and not quantity is the rational basis for administration, it seems less commonly appreciated that in point of standardizing the drug, activity is only one third of the problem Preparations of high degree of activity when tested by intravenous injection but practically inert by mouth in man,<sup>20</sup> due presumably to failure of absorption or too rapid elimination, are reported<sup>21</sup>

Pardee<sup>22</sup> investigated the subject in man with one specimen, determining elimination as has been done experimentally, in terms of persistence of action, arriving at the conclusion that the average daily elimination of digitalis in man is 22 minims of the tincture The activity of his preparation he reports, was 1.25 c c of the tincture to the cat unit Expressed in terms of a preparation with a cat unit of 0.75 c c, the average daily elimination should be about 13 minims of the tincture I have observed about seventy-five patients suffering with chronic cardiac disease and heart failure, requiring on the average about 30 minims a day of a preparation with the latter activity in order

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19 Eggleston, C Digitalis Dosage, *Arch Int Med* **16** 1 (July) 1915

20 Wedd, A M Observations on the Clinical Pharmacology of Digitalis, *Bull Johns Hopkins Hosp* **30** 131 (May) 1919

21 Eggleston, C, and Wyckoff, J The Absorption of Digitalis in Man, *Arch Int Med* **30** 137 (Aug) 1922

22 Pardee, H E B Notes on Digitalis Medication, *J A M A* **73** 1822 (Dec 13) 1919

11 The relation of delayed death following digitalis to the digitoxin-like fraction is discussed

12 In a starving animal, 0.1 mg of ouabain per kilogram is the fatal dose if the calculation is made on the basis of the average of the original and the new weights

*B Clinical*—1 Evidence is given to show that to determine elimination of digitalis in man several specimens must be employed

2 Clinical reports of digitalis persistence are strikingly in accord with experimental results and seem to indicate that, in man, tinctures of digitalis obtained from different sources are eliminated at different rates

3 The clinical significance of late digitalis death is set forth. The possibility of its occurrence days after the cessation of administration of the drug is suggested

4 Evidence is cited to show that the cat behaves in many respects similarly to man toward some of the digitalis bodies. The importance of an index of elimination in the standardization of the digitalis bodies for the more precise control of digitalis action is indicated

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tal bodies <sup>26</sup> In the cat, strophanthin is comparatively more rapidly eliminated than digitalis In man, a similar relation between strophanthin and digitalis is reported Cohn and Levy <sup>27</sup> found, in man, that the effects of the former rarely last more than five days, while the effects of the latter generally persist more than ten days Again, Hatcher <sup>28</sup> showed that the chloroform-soluble fraction of digitalis was readily absorbed from the gastro-intestinal tract of the cat Eggleston and Wyckoff <sup>21</sup> observed a similar behavior toward this fraction in man The clinical bearing of the differences found experimentally in the rate of elimination of the different digitalis preparations requires further study The electrocardiogram may help to solve the problem Should a relation be established, the problem of digitalization and its maintenance with a minimum of toxic reactions may be brought one step further within control

#### SUMMARY

*A Experimental*—1 A brief review of the literature relating to the fate of the digitalis bodies in the animal organism is given

2 The results of a study of digitalis elimination in the cat are reported in terms of persistence of action

3 The rate of elimination of digitalis varies with different specimens, the persistence of one may be several times that of another

4 Tolerance to the digitalis bodies probably depends on two factors (1) tissue immunity and (2) capacity for elimination

5 The digitalis bodies can produce an effect that persists independently to a degree of the presence of the drug

6 Digitoxin produces an effect that for a short time increases in intensity

7 The rapidly eliminated fraction does not exhibit this rising effect

8 The curve of digitalis elimination is complex and variable, depending on the resultant of action of the rapidly eliminated and the digitoxin-like fractions

9 The persistence of digitoxin as tested by the method of repeated dosage is considerably longer than that of the ordinary tincture of digitalis

10 Repeated doses of digitoxin or digitalis appear to sensitize to subsequent action of the drug The suggestion is offered that potentiation may, in part, account for so-called cumulation

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26 Levine, S A The Action of Strophanthin on the Living Cat's Heart, *J Exper M* **29** 485, 1919 Also Footnote 9

27 Cohn, A E, and Levy, R L A Comparison of the Action in Patients of G-Strophanthin and Digitalis, *Proc Soc Exper Biol & Med* **17** 81, 1920

28 Hatcher, R A Some Observations on the Pharmacology of a Digitalis Body, *J A M A* **75** 460, (Aug 14) 1920

# EFFECT OF INSULIN IN A CASE OF INCIPIENT DIABETIC COMA WITH RECOVERY

The effect of insulin on the clinical course of one case studied was so striking that it is worthy of note

A girl, aged 12, with a history of acute diabetes of three months' duration was admitted at 1 a m Dec 2 1922, into the service of Dr H A Laffeur, practically in coma. The urine markedly reduced Benedict's solution and gave a strong Ferric chlorid reaction for diacetic acid. The blood sugar was enormously increased (0.785 per cent). The plasma carbon dioxide combining power was 19.1 per cent by volume. Sixteen units of insulin were immediately administered, and the blood sugar, plasma carbon dioxide, urine sugar and acetone

TABLE 1—*Course of Author's Case, Case 6109*

Date	Time	Blood Sugar Percent age	Plasma Carbon Dioxide per Cent by Volume	Remarks
12/ 2/22	1 a m	0.781	19	Incipient coma
		16 units insulin		
	3 a m	0.561	24	Drowsiness less marked
	7 a m	0.310	28	Drowsiness less marked
		16 units insulin		
	11 a m	0.272	32	
	7 p m	8 units insulin		
12/ 3/22	9 a m	0.484	24	16 units 11 a m and 6 p m
12/ 4/22	9 a m	0.294	46	8 units 9 a m
12/ 5/22	9 a m	0.220	49	8 units 7, 11, 4, meals 9, 1, 6 (Wood yatt basal)
12/ 6/22	9 a m	0.185	52	8 units 7, 11, 4 meals 9, 1, 6 (Wood yatt basal)
12/ 7/22	9 a m	0.143	54	8 units 7, 11, 4, meals 9, 1, 6 (Wood yatt basal)
12/ 8/22	9 a m	0.095		8 units, 7, 11, 4, meals 9, 1, 6 (Wood yatt basal)
12/ 9/22	9 a m	0.226		No insulin given
12/10/22	9 a m	0.147		
12/11/22	9 a m	0.169		
12/12/22	9 a m	0.180		Taken 1½ hours after breakfast
12/13/22	9 a m	0.132		
12/14/22	9 a m	0.100		
12/17/22	9 a m	0.140		
12/19/22	9 a m	0.120		
12/22/22	9 a m	0.121		
12/23/22	9 a m	0.119		Discharged

bodies studied periodically as shown in Table 1. At 7 a m, six hours after the beginning of the treatment, during which two doses of insulin were administered, the drowsiness had practically disappeared. No food nor fluids of any kind, except water, were given during the next two days. The clinical picture was that of gradual improvement, and corresponding with this, improvement was shown by the laboratory data. On Dec 5, 1922, there was only a trace of acetonuria, and the child appeared to be out of any immediate danger of coma. There was still some glycosuria. A basal Woodyatt diet was then given, and small doses (8 units) of insulin administered three times a day, two hours before each meal. On Dec 7, 1922, the blood sugar was normal, the plasma carbon dioxide was normal, and the urine was free from sugar and acetone bodies. The insulin was then discontinued. Observations made daily during the following week on the blood and urine showed normal values, except for a slight degree of hyperglycemia, which eventually disappeared. The child was discharged from the hospital on Dec 22, 1922. Since then five weeks ago,



# OBSERVATIONS ON THE EFFECTS OF INSULIN IN THE TREATMENT OF DIABETES MELLITUS<sup>1</sup>

I M RABINOWITCH, M D  
MONTREAL, CANADA

My object is to present the data obtained in a number of cases of diabetes mellitus following the administration of insulin (These observations were made possible through the generosity of the diabetic committee of the University of Toronto who supplied this hospital with approximately 400 units of the extract weekly) The first experience we had was with a patient with severe diabetes, and it was soon found that the weekly supply of insulin would be sufficient to treat intensively only about one case a week For this reason the greater part of the insulin was applied to the study of various problems concerning the diabetic patient, and in only emergency cases was there any serious attempt made at treatment A number of patients with severe diabetes previously discharged were, therefore, readmitted for observation

I record the following observations

- 1 Effect of insulin on a case of incipient diabetic coma with recovery
- 2 Blood sugar time curves showing effect of insulin on the rate of fall of the sugar content of the blood
  - (a) Two hour curves
  - (b) One hour curves
  - (c) Fifteen minute curves
- 3 Effect of insulin on the blood sugar and acetone bodies, plasma carbon dioxide combining power, urinary excretion of sugar and ammonia, noted at short intervals
- 4 Effect of insulin on the respiratory quotient
  - (a) Average curve made from the respiratory quotients of twenty-four diabetic patients plotted with respect to glucose tolerance
  - (b) Curve of the daily respiratory quotients of a patient with severe diabetes treated with insulin
  - (c) Comparison of (a) with (b)
  - (d) Respiratory quotient time curve following ingestion of glucose in a diabetic patient
  - (e) Blood sugar time curve following ingestion of glucose in a diabetic patient
  - (f) Effect of insulin on (d) and (e) in the same person
- 5 Course of a patient on a diabetic diet, with and without insulin, in all the work the technical methods employed were
  - Blood Sugar—Lewis-Benedict method
  - Acetone bodies—Van Slyke method
  - Plasma carbon dioxide—Van Slyke method
  - Urine Sugar, qualitative—Benedict method
  - Quantitative—Benedict method for large amounts
  - Benedict-Osterberg method (1921) for small amounts
  - Total organic acid Van Slyke and Palmer methods

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\*From the Department of Metabolism of the Montreal General Hospital

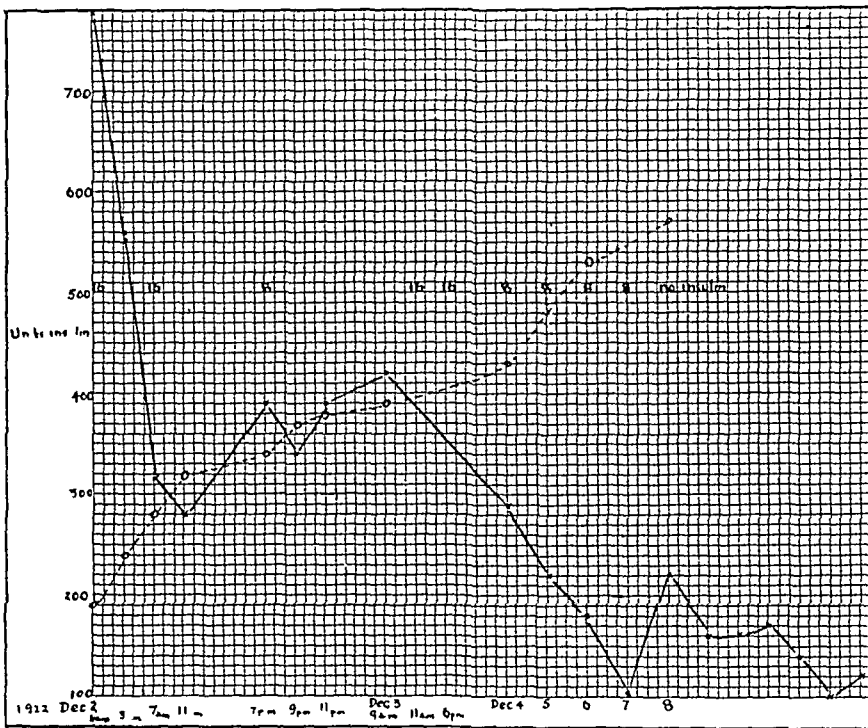


Chart 1—Incipient diabetic coma The continuous line is the blood sugar curve, per cent divided by 1,000, the broken line is the plasma carbon dioxide curve, per cent divided by 10 Insulin was given to the patient as follows on the sixth and seventh, 8 units were given at 7 and 11 a m and at 4 p m , on the eighth, 8 units were given at 7 a m only

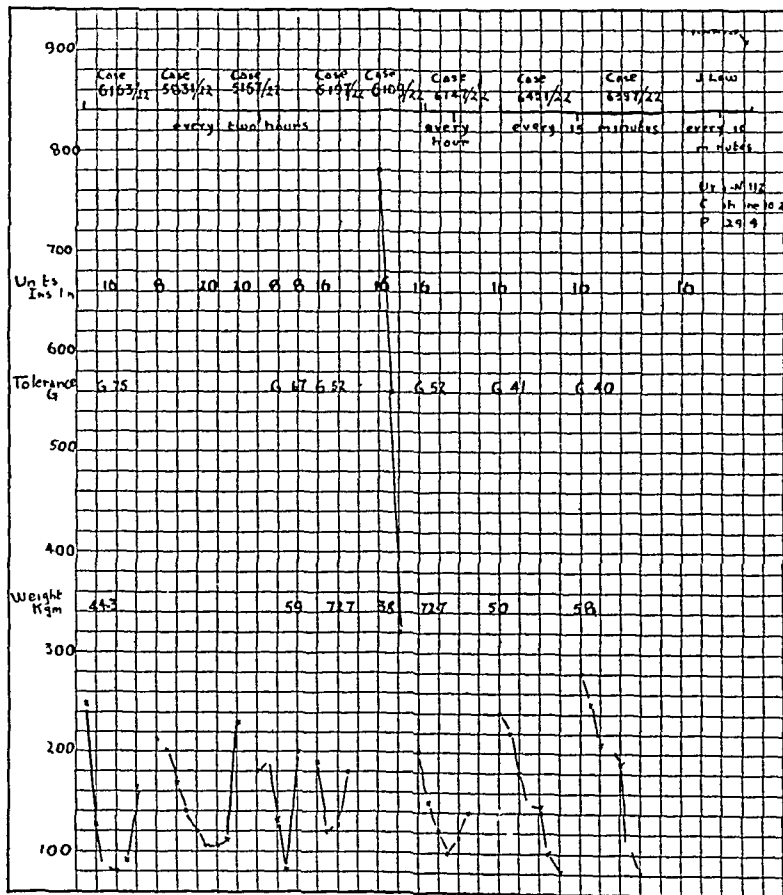


Chart 2—Blood sugar time curves following the administration of insulin The blood sugar is divided by 1,000

she has gained 10 pounds (4.5 kg), and the urine has remained sugar free and acetone free. The blood sugar examined weekly since has been normal. Chart 1 shows graphically the course of the case in detail. Table 1 shows the actual figures in detail.

### EFFECT OF INSULIN ON THE RATE OF FALL OF THE BLOOD SUGAR

A series of cases were studied with reference to the effect of insulin on the degree and rate of fall in the blood sugar. In all cases a constant amount of insulin was given (16 units). In Table 2 are given the

TABLE 2—*Blood Sugar Following Administration of Insulin*

Case Number	Units	Basal Period	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours	14 Hours
6163	16	0.239	0.129	0.084	0.081	0.094	0.167	
5831	16	0.212	0.204	0.163	0.166	0.144		0.232
5157	16	0.180	0.181	0.136	0.085			0.200
6197	16	0.195	0.120	0.126		0.180		
6109	16	0.781	0.561	0.310				
6163	8	0.167	0.052					
<hr/>								
6197	16	0.200	1 Hour 0.152	2 Hours 0.120	3 Hours 0.100	4 Hours 0.126	5 Hours 0.129	
<hr/>								
6451	16	0.235	15 Min 0.226	30 Min 0.185	45 Min 0.152	60 Min 0.148	75 Min 0.098	90 Min 0.086
6397	16	0.246	0.245	0.214	0.210	0.194	0.115	0.082

TABLE 3—*Effect of Insulin on Blood Sugar*

Case Number	Blood Sugar			Units	Weight, Kg	Glucose Tolerance, Gm	Fall in Blood Sugar	
	1	2	3				Mg per Kg	Mg per Unit
6109	0.781	0.561	0.220	16	38.0	30	5.71	13.7
5831	0.212	0.204	0.098	16	60.0	25	0.13	0.5
6397	0.277	0.115	0.162	16	58.0	40	2.76	10.1
6451	0.235	0.096	0.139	16	50.0	41	2.78	8.6
6197	0.194	0.120	0.074	16	72.7	52	1.01	4.6
5157	0.185	0.136	0.049	16	59.0	67	0.83	3.0
6163	0.239	0.129	0.110	16	44.3	75	2.48	7.8
	0.167	0.052	0.115	8			2.59	14.3

detailed results, and these are represented graphically in Chart 2. Blood sugar estimations were made in four cases every two hours, in one case every hour and in two cases every fifteen minutes. The temporary effect of insulin is shown in the two hour curves. That an immediate effect is obtained is shown in the fifteen minute curves. An attempt was made to determine whether the fall in the blood sugar was directly related to the body weight, dose of insulin or severity of the disease. The index of the latter was taken as the glucose tolerance determined by the Woodyatt method ( $G = C + 0.1 F + 0.58 P$ ). In Table 3, it will be noted that no correlation could be found in the cases studied. This at the time of the observations was attributed to the

graphically represented in Chart 3. The most rapid changes noted were in the fall of urinary excretion of sugar and titratable acid plus ammonia. The graphic chart suggests an increase of the latter during the second hour. If, however, the total of the four fifteen minute periods are added together, it will be noted that the excretion was much less during the second than during the first hour. The rise in the carbon dioxide combining power of the blood was not inversely in proportion to the fall in the excretion of titratable acid plus ammonia, nor to the fall of the concentration of acetone bodies in the blood. The body was thus apparently able to oxidize the acetone bodies much more rapidly than

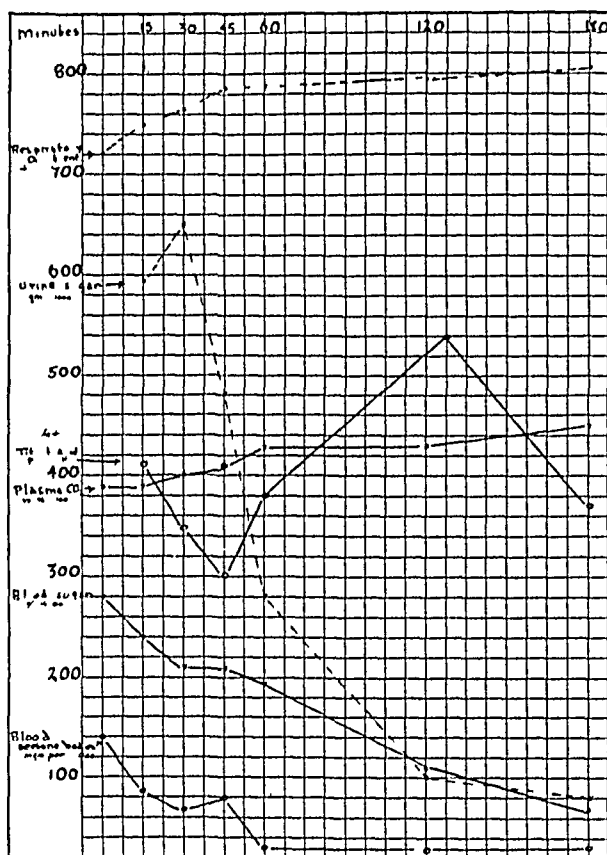


Chart 3—Effect of insulin on blood sugar, blood acetone bodies, plasma carbon dioxide, urine sugar, urine acetone bodies and respiratory quotient

it could mobilize alkali. When all other factors are considered which may effect a rise in the respiratory quotient during so short period determinations by indirect calorimetry, it is difficult to interpret the respiratory quotient curve obtained in this case. Since this diabetic patient had a severe acidosis, the rise in the respiratory quotient may be partly attributed to the oxidation of the acetone bodies.

#### RESPIRATORY QUOTIENTS

Some observations were then made on the respiratory quotients since the latter offers the best index to the replacement of fat and protein

possible variation in the potency of the individual preparations used. This was strongly suggested in the last case, No 6163, in which 8 units produced practically the same fall that 16 units produced in the same person one week previously. The latter result was, however, attributed by Dr Banting<sup>1</sup> to the fact noted by him, that the effect of insulin may vary in the same person at different stages in the treatment. In one patient (J Low) admitted in the last stages of diabetic coma, no change was noted in the blood sugar following the administration of 50 units of known potent preparation. This case was, however, complicated by surgical lesions of both kidneys associated with complete anuria. The blood urea nitrogen was 112 mg per 100 c c, creatinin 10.2 mg and phosphorus 29.4 mg per 100 c c of blood. This may partly explain the enormous degree of hyperglycemia—1,000 per cent. Blood sugar estimations made every ten minutes for one hour showed practically no fall. The patient died one and one-half hours after admission to the hospital.

EFFECT OF INSULIN ON THE BLOOD SUGAR AND ACETONE  
BODIES, PLASMA CARBON DIOXID COMBINING POWER,  
URINARY EXCRETION OF AMMONIA AND SUGAR  
AND THE RESPIRATORY QUOTIENT

Since a definite fall in the blood sugar was noted every fifteen minutes, observations were then made on a severe diabetic patient (Woodyatt G = 40) at short intervals on the effect of insulin on the

TABLE 4—*Effect of Insulin on a Patient with Severe Diabetes, Case 6397*

Time	Respiratory Quotient	Titrate Acid Plus Ammonia C c N/10	Urine Sugar, Gm	Blood Sugar Per centage	Plasma Carbon Dioxid, Percentage by Volume	Blood Mg per 100 C c	Remarks
9 30	0.724			0.277	39.3	104.2	16 units insulin
9 45	0.750	41	0.596	0.243	39.6	86.7	
10 00	0.764	36	0.640	0.217	40.2	72.6	
10 15	0.782	30	0.482	0.212	40.8	74.3	
10 30	0.786	38	0.276	0.192	42.4	56.4	
11 30	0.793	54	0.107	0.115	42.2	43.8	
12 30	0.804	37	0.177	0.080	44.4	39.3	

blood sugar and acetone bodies and plasma carbon dioxide combining power, urinary excretion of sugar and ammonia and the respiratory quotient. (The technic of determining the latter, and the precautions taken in the interpretation will be described under the section on the respiratory quotient.) The effect of the insulin in this case was almost immediate. In Table 4 are shown the detailed results, and these are

1 Personal communication

if the cases are grouped with respect to their tolerance, for example,  $G = 50 - 75$ ,  $75 - 100$ ,  $100 - 125$ , etc., the tolerance for the group is greater, and a greater average respiratory quotient is obtained, that is, it is reasonable to assume the less severe the diabetes, the more the patient is able to store glycogen in the body and thus show a greater respiratory quotient in the postabsorptive state—fifteen hours after

TABLE 5—Average Respiratory Quotient Obtained in Normal Persons

Normal Respiratory Quotients			Comparison of the Tolerance of Glucose With the Respiratory Quotient in Diabetic Persons		
Case Number	Basal Metabolic Rate	Respiratory Quotient	Case Number	Glucose Tolerance (Woodyatt)	Respiratory Quotient
6427	4	0.816	1739	56	0.714
6497	2	0.814	2602	58	0.792
6373	6	0.836	4146	62	0.732
6100	2	0.809	955	63	0.714
6286	1	0.798	818	66	0.719
5958	7	0.817	543	72	0.768
5741	9	0.842	5135	77	0.730
5658	7	0.810	1157	82	0.761
6210	3	0.826	90	81	0.729
6068	2	0.836	844	85	0.742
6148	2	0.767	252	96	0.782
6100	2	0.827	704	98	0.803
6161	11	0.901	1193	104	0.796
5751	5	0.831	352	111	0.794
6063	2	0.906	1700	116	0.732
5957	3	0.811	910	129	0.787
4969	6	0.795	1154	132	0.823
5021	5	0.831	5601	147	0.746
5792	3	0.759	2423	169	0.761
5100	5	0.792	5642	216	0.826
			2303	219	0.799
			2968	235	0.838
			5961	240	0.801
Average		0.811	6055	242	0.814

TABLE 6—Results of Administration of Insulin in Case 6163

	Respiratory Quotient	Remarks
Basal	0.752	No insulin
December 8	0.762	8 units 7 a m, test, 9 a m
9	0.748	No insulin
10	0.734	No insulin
11	0.778	8 units, 7 a m
12	0.769	8 units, 7 a m
13	0.781	8 units, 7 a m
15	0.761	8 units, 7 a m
16	0.779	1 unit before meals
17	0.792	4 units before meals
18	0.798	4 units before meals
20	0.787	1 unit 7 a m only
21	0.795	8 units 7 a m only

the evening meal. If this assumption is even approximately correct, a patient who can take more food while under the effects of insulin and can store part of it should show a greater quotient in the post-absorptive state if storage has actually occurred. The results obtained in the one case reported here suggests that there has been a storage of carbohydrates. In Table 6 will be seen the detailed results. The patient was kept under the influence of insulin for a period of two

metabolism by glucose In a diabetic patient the interpretation of results obtained are complicated by the fact that the acetone bodies give approximately the same respiratory quotient as carbohydrate, fat and protein Thus

<i>Substance</i>	<i>Respiratory Quotient</i>
Carbohydrate	1
Diacetic acid	1
Protein	0.81
B-oxy-butyric acid	0.89
Fat	0.71
Acetone	0.75

In order to avoid this complication in the interpretation of results for these studies, the only diabetic patients observed were those whose urine was acetone free and plasma carbon dioxide normal All determinations were made with the Tissot apparatus and half-face Siebe-Gorman mask Gas analyses were made with the Haldane apparatus In spite of the many disturbing factors which might influence the respiratory quotient by the method used, such as short period observations, abnormal breathing (mask), rapid washing out of carbon dioxide due to temporary increased pulmonary ventilation at the moment the venous punctures were made, etc., the results obtained are significant qualitatively of the effect of insulin on storage and utilization of sugar It is generally accepted that a diabetic patient has no difficulty in obtaining sugar from the usual precursors, it is from the disproportion between formation, utilization and storage that the hyperglycemia results The results obtained with insulin show that storage plays a great part in the control of the hyperglycemia during the treatment with insulin

The routine in the determination of all the respiratory quotients recorded here, with the exception of the time curves obtained following the ingestion of glucose, were made under the accepted standard conditions—in the postabsorptive state fifteen hours after the evening meal and after one-half hour of complete muscular rest

In Table 5 is shown the average respiratory quotient obtained in twenty normal persons During the last year some data were obtained concerning the relation between the glucose tolerance of the patient determined by the Woodyatt method ( $G = 0.1 F + 0.58 P$ ) and the respiratory quotient obtained fifteen hours after the evening meal The results are recorded in the same table It will be noted that although in isolated instances a patient may show a greater respiratory quotient than another whose tolerance is greater (Cases 818 and 543),

metabolism, that is, they were not of the nonprotein type. This is rather unfortunate. But the difficulty of obtaining a specimen of urine at the end of such small periods made the obtaining of non-protein figures impossible. For practical purposes, however, this does not vitiate the results obtained, since qualitative values only were sought, a rise in the quotient indicating carbohydrate oxidation, etc.

The subject of one experiment had a mild diabetes. During the postabsorptive state and under standard conditions for basal metabolism studies, the respiratory quotient and blood sugar were determined. The

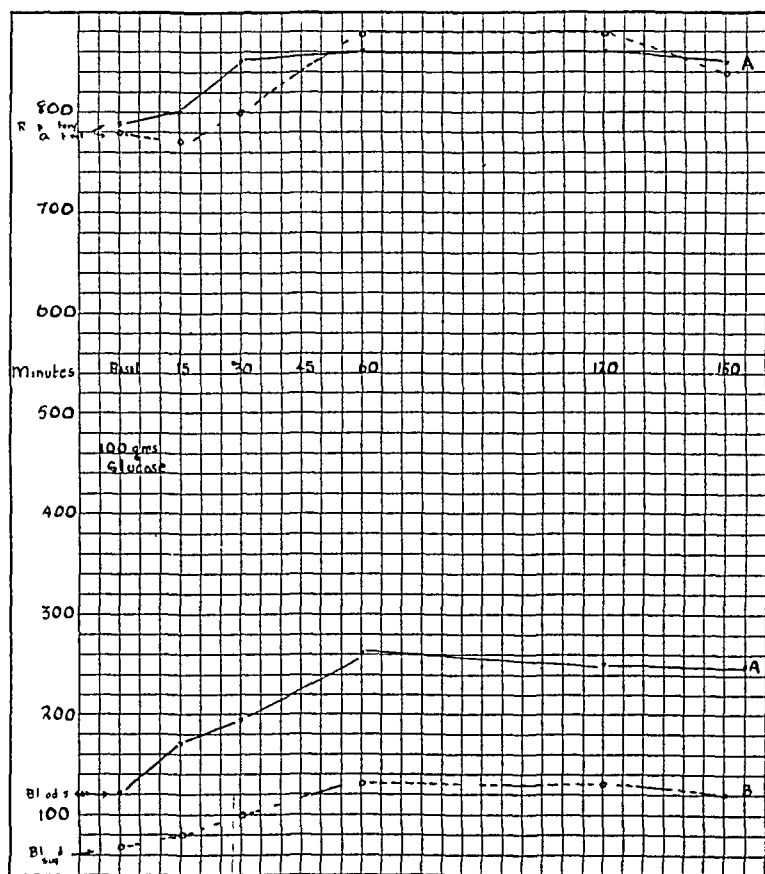


Chart 5—Effect of insulin on blood sugar and respiratory quotient following ingestion of glucose in a "sugar free" diabetic patient. *A* indicates no insulin, *B*, 16 units of insulin one-half hour before ingestion of glucose, the blood sugar was divided by 1,000, respiratory quotient, 1,000.

subject was then given approximately 1.75 gm of glucose per kilogram dissolved in 250 c c of water flavored with lemon. The face mask was then immediately adjusted, and the blood sugar and respiratory quotient estimations were made at the intervals stated in Table 7, which gives the detailed results. The time recorded represents the end of each experiment, the gas collection in the gasometer commencing ten minutes previously. In Chart 5 the results are recorded graphically. Curves *A*



weeks His original tolerance before administration of insulin was 75 gm glucose (Woodyatt) While under the influence of insulin the diet could be increased to a glucose tolerance of between 125 and 150 The respiratory quotient was determined daily The results noted are graphically shown in Chart 4 Curve *A* represents that of the average respiratory quotient of the different groups of cases with respect to their tolerance of glucose,  $G=50-75$ ,  $75-100$ , etc, shown in Table 5 The dotted curve is that of the patient's daily respiratory quotient It will be noted that at the end of two weeks the patient had acquired a respiratory quotient corresponding to that of a person whose tolerance would be approximately 175

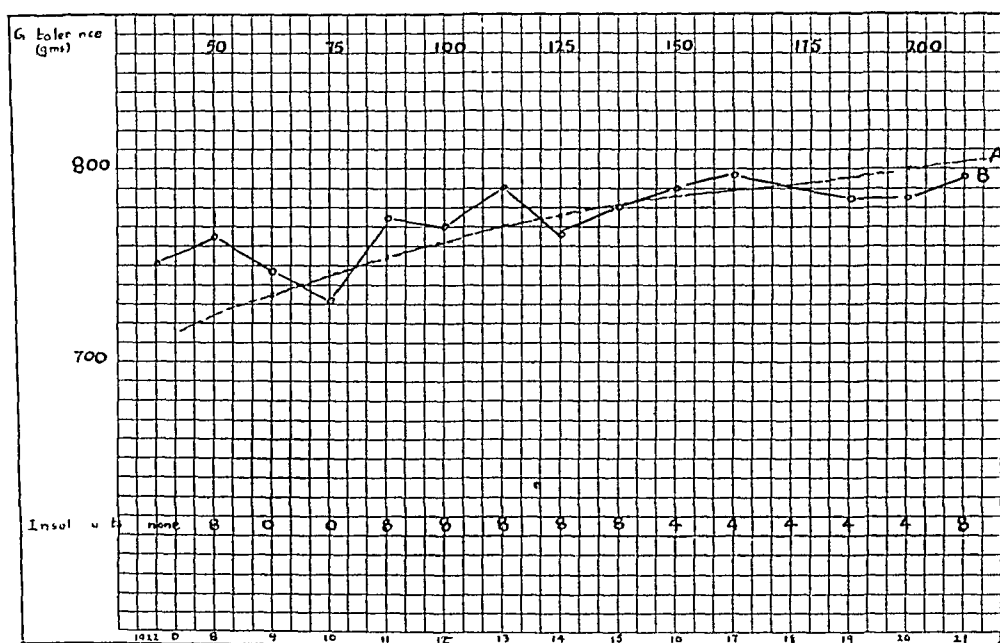


Chart 4—Effects of tolerance for glucose and insulin on the respiratory quotient *A* is the average curve, *B*, Case 6163 The respiratory quotient is divided by 1,000 On December 8, 8 units of insulin were given at 7 a m, on the eleventh, twelfth, thirteenth, fourteenth and fifteenth, 8 units of insulin were given at 7 a m, on the sixteenth, seventeenth, eighteenth, nineteenth and twentieth, 4 units were given three times a day, and on the twenty-first, 8 units were given three times a day

That storage is a definite phenomenon observed under the influence of insulin is further demonstrated when the sugar tolerance and respiratory quotient time curves are correlated in the same person following the ingestion of glucose

In the foregoing analyses all the respiratory quotient figures represent nonprotein values In the following analyses in which sugar time curves were simultaneously obtained, the respiratory quotients were obtained directly without taking into consideration the protein

hydrates into fats, unaccompanied by actual combustion of carbohydrate. It was thought that the rise might be due to some of the factors mentioned before, for example, disturbance of the patient due to venous puncture, etc. It will be noted, however, that practically a corresponding rise (Curve *B*) was obtained in the same person at a later date when no venous punctures were made. In Chart 6 are recorded graphically the two curves—Curve *A* obtained during venous puncture and Curve *B* under more ideal conditions, that is, the glucose only was given and the respiratory quotient obtained at the stated intervals. It seems possible that a patient with severe diabetes will burn rather than store the little carbohydrate he is capable of tolerating.

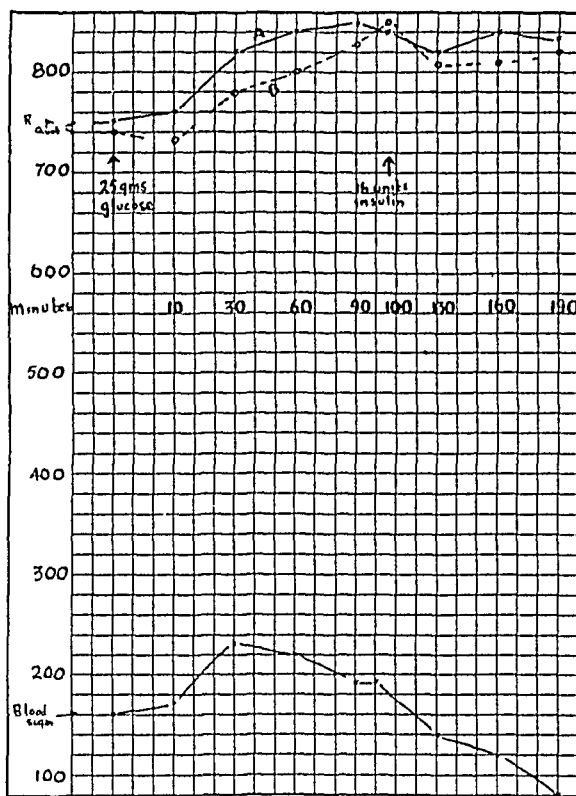


Chart 6—Effect of insulin on blood sugar and respiratory quotient following ingestion of glucose in a “sugar free” diabetic patient. Curve *A* was taken during the blood sugar time curve determination, *B* was taken seven days later the blood sugar was divided by 1,000, the respiratory quotient by 1,000.

Further studies of the effect of small doses of glucose on the respiratory quotient in the diabetic patients are now being undertaken in this hospital.

#### EFFECT OF DIET ON A PATIENT WITH SEVERE DIABETES WITH AND WITHOUT INSULIN

Chart 7 demonstrates definitely the possible sources of danger when diet and insulin are combined in the treatment, and impresses one with the important fact that insulin treatment has not yet reached the stage

represent a test during which no insulin was given. Curves *B* represent the results obtained in the same person a few days later, but one hour before the test 16 units of insulin were administered. Although the same dose of glucose was given in the second test, the blood sugar curve did not differ from that usually obtained in normal persons. In spite of this, there was no great change noted in the respiratory quotient curve. Storage is thus suggested. There is, however, a possibility of delayed absorption of the glucose from the alimentary tract. The fact that a rise in the quotient was obtained without insulin and that during

TABLE 7—*Results of Administration of Insulin in a Patient with Mild Diabetes Case 6497*

Dec 8, 1922—No Insulin Given							
	Basal	15 Min	30 Min	60 Min	120 Min	150 Min	180 Min
Respiratory quotient	0.791	0.799	0.851	0.863	0.869	0.852	0.870
Percentage of blood sugar	0.121	0.172	0.196	0.260	0.250	0.247	0.240
Urine sugar	0	0	Trace	+	+	+	Trace

Dec 15, 1922—Sixteen Units of Insulin Given One Hour Before Test							
	Basal	15 Min	30 Min	60 Min	120 Min	150 Min	180 Min
Respiratory quotient	0.781	0.779	0.794	0.875	0.882	0.847	0.840
Percentage of blood sugar	0.071	0.080	0.098	0.136	0.130	0.119	0.114
Urine sugar	0	0	0	0	0	0	0

TABLE 8—*Results of Administration of Insulin in a Patient with Severe Diabetes, Case 6163*

Dec 6, 1922—Sixteen Units Given at End of 90 Minutes									
	Basal	10 Min	30 Min	60 Min	90 Min	100 Min	130 Min	160 Min	190 Min
Percentage of blood sugar	0.164	0.180	0.232	0.226	0.194	0.191	0.145	0.120	0.098
Urine sugar, gm		0.042	0.071	0.121	0.052	0.049	0.060	0.074	
Respiratory quotient	0.750	0.764	0.820	0.841	0.849	0.840	0.831	0.839	0.835

Dec 13, 1922—Sixteen Units Given at End of 90 Minutes									
	Basal	10 Min	30 Min	60 Min	90 Min	100 Min	130 Min	160 Min	190 Min
	0.742	0.735	0.735	0.809	0.832	0.849	0.813	0.810	0.820

this rise the hyperglycemia persisted in the first test, suggests defective storage in the absence of insulin.

In Table 8 are recorded the results of the same experiment obtained in a patient with much more severe diabetes. In this case much less glucose was given, 25 gm, or 0.5 gm per kilogram. A definite rise in the quotient was noted. In the fasting normal persons, judging from the literature on the subject, no rise occurs in the metabolism following ingestion of such small amounts of glucose on account of the retention of the latter in the organism in the form of glycogen. Even the rise occasionally noted has been attributed to the conversion of the carbo-

the general condition of the patient and laboratory findings were just as marked. Thus the ability to utilize carbohydrates in this case was not due to an improved pancreatic function, but directly to the effect of the insulin.

#### DISCUSSION OF TREATMENT

The experience we have had demonstrates that the reaction of a series of patients with diabetes to insulin is not uniform. Injection of the extract isolated by the Toronto group of workers lowers the sugar content of the blood. It does so in such a manner as to enable the diabetic patient to metabolize more sugar. Thus it aids the complete oxidation of fat, preventing the formation of acetone bodies, or making them disappear when present. The effect, however, is temporary. Its chief value, in the present status of our knowledge of its action, seems to lie in tiding over the diabetic during the critical stage of the disease (precoma), so difficult to control with the usual procedures, fasting, intravenous injections of salines, etc. In patients with severe diabetes, emaciated, and in whom protein plays a great part in the formation of energy, and who progress best when controlled by a diet on the Woodyatt basis, with the administration of insulin the diet may be increased to the point where the patient gains weight and generally shows clinical improvement. Diet still remains the important means of controlling the disease. The ultimate type of treatment to follow, whether diet alone or diet plus insulin, seems to depend on whether the pancreatic function is completely destroyed as in pancreatic diabetes, or whether the little remnant is only temporarily overstrained, but can recover with rest. A case of the latter type seems to be the first one recorded here. The fact that the child has recovered under the effects of insulin, but does not now require the extract, diet alone sufficing, seems to prove that the pancreatic function was not completely destroyed but temporarily overstrained. The possibility of the development of "carbohydrate shock" associated with an hypoglycemia was emphasized by the Toronto workers. It has been suggested, where large doses of insulin are required, to give just sufficient of the latter to allow a constant slight trace of glycosuria. This, however, appears to be contrary to treatment that might lead to an improved pancreatic function. If traces of sugar are constantly present in the urine, it seems reasonable to assume that the full effect of the insulin given is made use of, but in spite of this the pancreatic function is also called on and strained. Allen has demonstrated that recuperation of pancreatic function can be negated by overfeeding. Lack of thoroughness in relieving the food load is the chief factor in the deterioration of the little function left. The various responses obtained from insulin emphasize the statement of Sir John Rose Bradford that

where it can be applied in outside practice without being controlled carefully by laboratory analyses. The curve represents the course in a patient with severe diabetes (G, 45) who was discharged from the hospital in October, 1922. The urine was then sugar and acetone free. The blood showed only a slight hyperglycemia. The patient could be kept sugar free while on a Woodyatt diet, but was in a nutritional state much below normal. He was readmitted Dec 10, 1922, to note the effect of insulin. Until December 16, the diet was the same as that which he was allowed on discharge. It will be noted that the total quantity of sugar excreted during the twenty-four hours was practically normal, about 1 gm, and only a slight hyperglycemia was present,

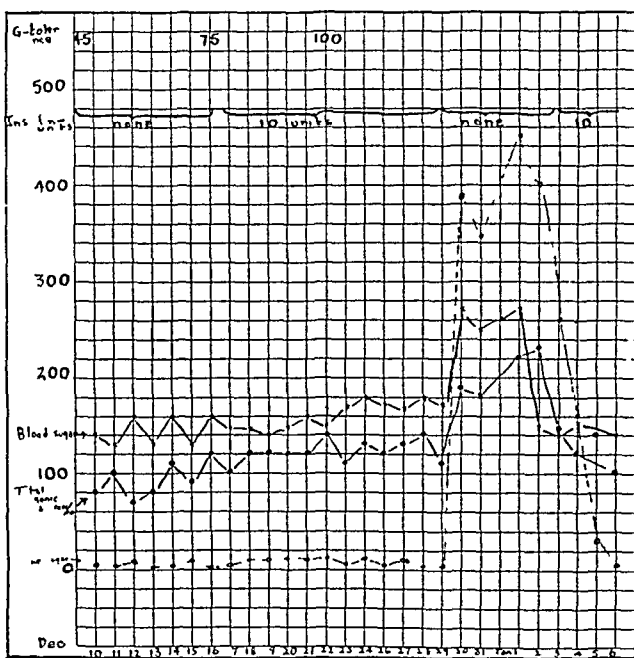


Chart 7—Diet with and without insulin. The blood sugar was divided by 1,000, the urine sugar by 10, the total organic acids by 10.

approximately 0.150 per cent. Ten units of insulin were given three times a day, one hour before each meal, on December 16, and the diet was increased to  $G=75$ . No great change was noted, either in the hyperglycemia or in the excretion of sugar. On December 23, the diet was further increased to  $G=100$ . The same dose of insulin was continued. There followed an increase in the degree of hyperglycemia and a small increase in the excretion of sugar in the urine. On December 29, the supply of the extract was exhausted. The results which followed were striking. A marked hyperglycemia and glycosuria developed, and the excretion of organic acids increased. On Jan 2, 1923, insulin treatment was again instituted, and the improvement in

## THE IMPORTANCE OF OUR KNOWLEDGE OF THYROID PHYSIOLOGY IN THE CONTROL OF THYROID DISEASES \*

DAVID MARINE, M A, M D  
NEW YORK

### PHYSIOLOGY OF THE THYROID

When we realize that our definite knowledge of the function of the thyroid gland dates from 1874, when Sir William Gull published his clinical pathological study, "On a Cretinoid State Supervening in Adult Life in Women," all will agree that much progress has been made during the nearly fifty years that we have followed its publication. While today we can boast that we are able to reproduce experimentally, to diagnose, and to treat myxedema successfully, and that we can with certainty prevent endemic goiter and endemic cretinism, it must still be admitted that our knowledge of the rôle of the thyroid gland in human physiology and pathology is yet in its infancy. Our lack of knowledge concerning the thyroid applies particularly to its influence on other glands of internal secretion and their influence on it. We probably possess a more detailed knowledge of the anatomy, physiology, chemistry and pathology of the thyroid than of any other gland, and I shall attempt to review as briefly as possible some of the more important facts of thyroid physiology and their application to the problem of the control of thyroid disease.

The major function of the thyroid, as we now know it, is to provide a means through its iodine-containing hormone for maintaining a higher rate of metabolism than would otherwise exist and for varying this rate. The gland is not essential for the vegetative life of adult animals. In the young it is necessary for growth and differentiation. Thyroid removal in animals causes a lowering of metabolism (measured as heat production) as much as 40 per cent, which is comparable to the maximum decrease seen in the severest forms of human myxedema. This decrease in metabolism begins usually on the sixth or seventh day after removal, and in cats and rabbits reaches its maximum about the twentieth day after removal, as shown in Figure 1. The reduction in metabolism is permanent if the thyroid is completely removed, but if,

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\* Eighth Mellon lecture delivered before the Society for Biological Research, University of Pittsburgh, May 10, 1923

diabetes is "a clinical label attached to a number of different conditions with varied origins, different morbid anatomy and physiology and liable to different courses" There is much more to learn of this disease The efforts made and results obtained by Dr Banting and his associates have opened a new field for study, but, most essential of all, they have resulted in the possibility of prolonging life and making it more worth living

1895, causes a striking increase in heat production. Fourthly, thyroid removal causes a decrease in heat production. These facts constitute sufficient evidence that the thyroid plays an important part not only in the maintenance of a given basal rate of metabolism but also in providing a means, through fluctuation in its activity, for varying this rate. There is some evidence also that the thyroid is an important factor in the increased heat production accompanying bacterial infections.

Magnus-Levy, in 1895, showed that in Gull's disease heat production was decreased, while in exophthalmic goiter it was increased. Also in 1895, Baumann announced that iodine was a normal constituent of the thyroid, and subsequent work has established the fact that the thyroid exerts its influence on metabolism by means of the very stable iodine containing hormone which Kendall in 1916 isolated in crystalline form and gave the name thyroxine. This hormone is intimately associated with the globulin of the colloid, from which it is separated only by destructive hydrolysis, and is stored in the colloid material of the alveoli in variable amounts. The colloid or globulin appears to act as a vehicle for storing the reserve of this very active hormone. Measured as iodine, the maximum store in the normal human thyroid is around 25 mg., or approximately 1 mg. per gram of fresh gland. The thyroid gland has an extraordinary affinity for iodine both *in vitro* and *in vivo*. The iodine content may be increased several hundred per cent. within five minutes after the injection of 50 mg. of potassium iodide into the femoral vein of a dog. The administration of iodine in any form in any manner causes the store to be increased to the maximum. This is true for the human thyroid as well. Such rapidly stored iodine is at first inactive, but the transformation to the active form can be demonstrated in dogs in about twenty-four hours by means of the tadpole test. The fact that there is no fixed ratio between the active and the inactive iodine probably indicates that the active iodine is slowly elaborated from the inactive iodine taken from the blood stream and either discharged into the circulation or stored in the colloid.

The functional activity of the gland is controlled chemically mainly through the blood stream but perhaps also indirectly through the sympathetic nervous system. The functional capacity of the gland is not impaired by sectioning the nerves running in the adventitial coats of the vessels and encasing the gland in paraffin. Thyroid tissue autotransplanted in any part of the body shows the same capacity for hyperplasia, involution and the storage of iodine as is exhibited by the normal gland. If bits of the thyroid are removed from the neck and transplanted into the ear, the abdominal wall, and the ovary, these transplants show morphologic and chemical changes similar to those occurring in the nontransplanted tissue. Thus, if the nontransplanted thyroid tissue is undergoing hyperplasia, the transplants, wherever



as usually happens, fragments or accessories remain, regeneration occurs and the metabolism rises again, in some instances, to normal. We have observed rabbits in which the metabolism has remained 20 and 30 per cent below normal for three years or approximately one half the average life of this animal.

That the thyroid gland provides the means for varying the rate of heat production can be shown in several ways. First, it has been shown in animals that sufficient but sublethal injury to the suprarenal glands causes a marked chronic increase in heat production, provided the thyroid gland is intact, but thyroid removal prior to injuring the

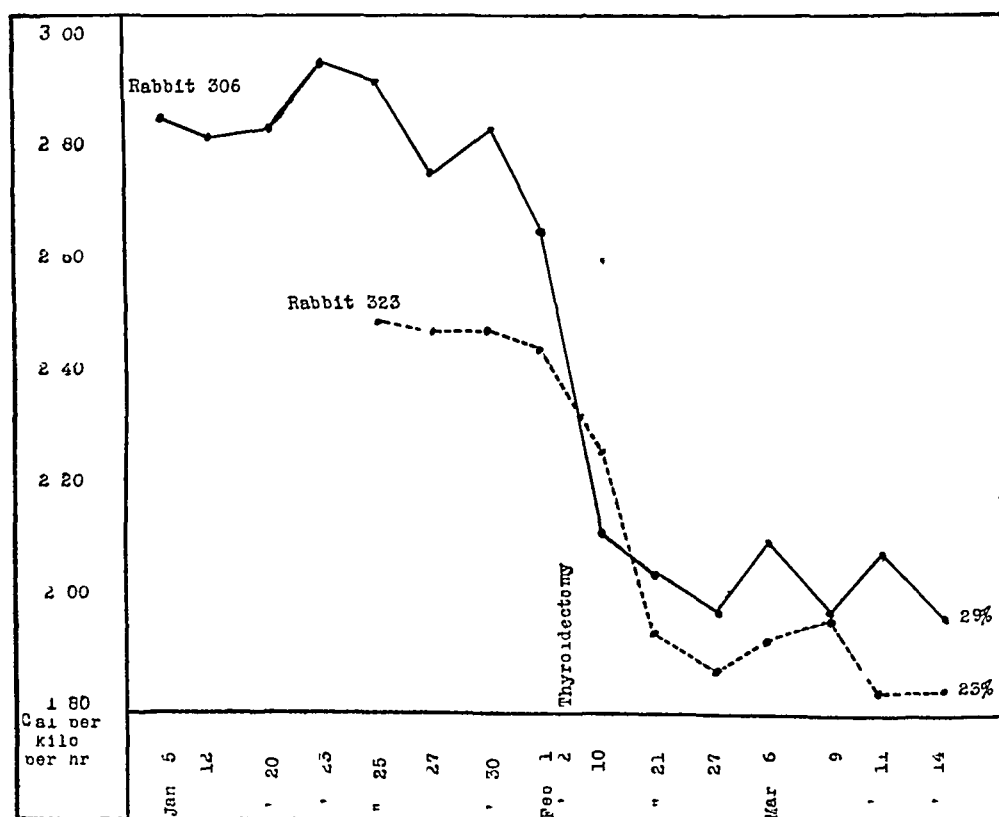


Fig 1—Thyroidectomy and heat production

suprarenal glands greatly reduces or abolishes the increase. Secondly, in all mammals studied there is a marked rise in heat production during pregnancy and lactation. In the rabbit, this increased heat production begins about the middle of pregnancy and continues through the period of lactation. Thyroidectomy in the rabbit abolishes or greatly reduces this normal rise in metabolism. This relation of the thyroid to the increased heat production of pregnancy and lactation probably has an important bearing on thyroid enlargements (goiters) occurring during pregnancy and lactation and will be referred to again. Thirdly, the administration of thyroid glands, as first shown by Magnus-Levy in

This generalization could readily be tested experimentally by studying the effects of administering and withholding iodine after partial removal of the thyroid. As has been shown by many observers, notably by Wagner, Halsted and Ribbert, if one half to three quarters of the gland is removed, the remainder undergoes compensatory hyperplasia histologically identical with the spontaneous hyperplasias seen in developing goiters. Marine and Lenhart have carried out large numbers of experiments of partial removal, comparing the histologic appearance and iodine store, and it was found that compensatory hyperplasia did not begin until the iodine store in the remaining part had fallen below 0.1 per cent, and that the degree of compensatory hyperplasia increased proportionately as the iodine store decreased, just as was found in the spontaneous hyperplasias. Conversely, if one removes as much as three fourths of the gland and administers traces of iodine (from 1 to 2 mg. weekly), no compensatory hyperplasia takes place in the remaining portion such as would regularly occur if iodine was withheld. The administration of desiccated thyroid will protect the thyroid against compensatory hyperplasia even after the removal of five sixths of the gland. These very simple experiments show clearly that the changes in the iodine store and histologic structure occurring in experimentally controlled hyperplasia are identical with those occurring in spontaneous hyperplasia or goiter.

The same general reaction of the thyroid can also be produced in experimental congenital goiter. The late Professor Halsted first experimentally produced congenital goiter in dogs in 1889. He observed that the puppies born from mothers that had had most of the thyroid gland removed had enlarged actively hyperplastic glands, reaching twenty times the normal size. He noted also that the histologic appearance of such congenital goiters was identical with the compensatory hyperplasia following partial removal of the gland. The fact that removal of most of the thyroid from the mother ordinarily causes marked enlargement of the fetal thyroid has been confirmed from many sources and for many of the experimental laboratory animals, including the dog, the cat, the sheep and the rat. In addition to confirming Halsted's observations on these animals, we have added the additional fact that if one gives a few milligrams of iodine during pregnancy to cats and dogs from which most of the thyroid has been removed, the young at birth will have thyroids normal as to weight, histologic structure and iodine content. We have also been able to obtain from the same animal alternate litters of goiterous and nongoiterous young, merely by withholding or administering iodine. These experimental congenital thyroid hyperplasias are true congenital goiters. They are identical with the spontaneous congenital goiters of man and animals and are dependent on a maternal functional insufficiency of the thyroid. As in many other

located, show hyperplasia of similar degree, and if iodine is administered the transplants show the same involution and storage of iodine as occur in the nontransplanted gland

The thyroid gland exhibits great variations in functional activity to meet the wide variations in metabolism occurring during the life of the animal, particularly in the female. For example, there are variations due to season. Seidell and Fenger have shown the increase in the iodine store during the summer months and its decrease during the late winter and early spring months. Many observers have noted the increased incidence of thyroid enlargement (goiter) during the winter and spring months. There is a notable increase in thyroid activity at puberty, during pregnancy and lactation, during the menopause, during protracted febrile reactions (tuberculosis and syphilis), and following the prolonged use of certain diets, particularly those with a high fat and protein content. It might be pointed out that these conditions, in which the thyroid activity is known to be increased, correspond as regards time to the periods in life when thyroid enlargement or goiter develops. Increased thyroid activity is associated with a decrease in the iodine store in the gland, provided the intake of iodine at such times is not correspondingly increased, and if the iodine store falls below 0.1 per cent, thyroid enlargement begins. The morphologically normal thyroid contains on the average about 0.2 per cent iodine. The maximum store is between 0.5 and 0.6 per cent and the minimum store associated with normal gland structure is about 0.1 per cent. The thyroid gland is endowed with an enormous capacity for growth, which provides a factor of safety and a compensatory mechanism to meet increased functional demands. These enlargements of the thyroid are familiar to all of us as ordinary goiter.

In comparing the microscopic appearance and the iodine content of the thyroid glands of several hundred dogs and of human beings, a striking relationship between the iodine store and the histologic structure was made out. In the thyroids with normal structure the iodine content varied between 5.5 mg and 1 mg per gram of dried gland. When the iodine store was below 0.1 per cent, hypertrophic and hyperplastic changes were regularly found. In comparing further the varying degrees of thyroid hyperplasia with the iodine store of such glands, it was found that the iodine store progressively decreased as the degree of hyperplasia increased, so that in the most marked hyperplasias, iodine was usually absent or present only in traces. A similar relationship between the iodine store and the histologic structure of the gland has been observed in large series of thyroid glands of ox, pig, sheep and fowl. The generalization may therefore be made that the iodine store varies inversely with the degree of active hyperplasia, and that if the iodine store is higher than 0.1 per cent, no hypertrophic changes are present.

Finally, experiments were undertaken to demonstrate that the normal thyroid could be kept normal for long periods of time, even in highly goiterous districts, merely by the administration of traces of iodine. In these experiments, litters of puppies from iodized mothers were used in order to insure normal thyroids at birth. To half of each litter, 1 mg. of iodine was given by mouth once a week while the other half of each litter served as controls. These experiments were carried out in Cleveland, where practically all dogs normally have some degree

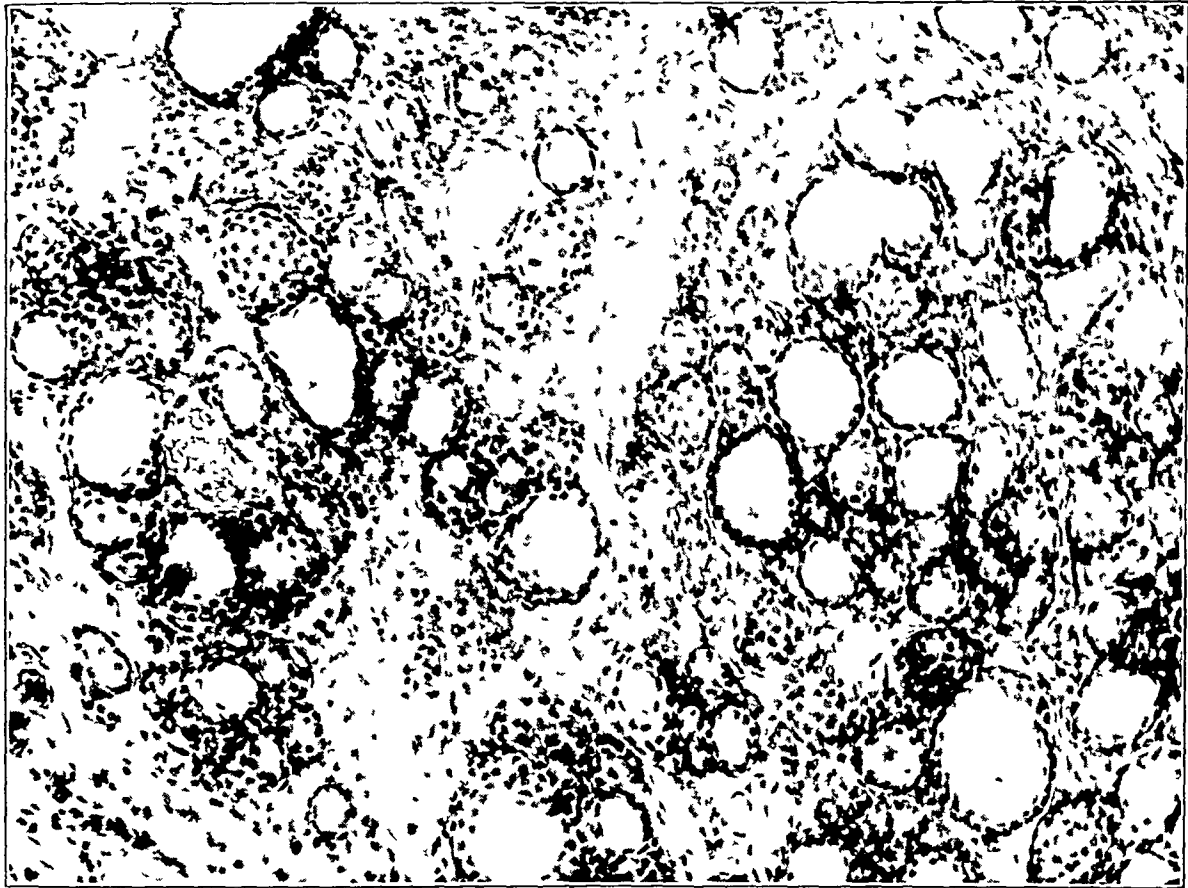


Fig 3—Section of the same thyroid removed Dec 17, 1908, showing marked decrease in stroma and a corresponding relative increase and more differentiation of the alveoli

of thyroid hyperplasia. It was found that those puppies that did not receive iodine developed thyroid hyperplasia, while the thyroids of those that received the milligram once a week remained normal, although the iodized and control puppies were kept in the same kennels and fed with the same kind of food. These experiments proved that iodine did control thyroid overgrowth, and that we had to deal with a unique physiologic fact in that a single inorganic element prevented overgrowth of the gland and controlled the functional value of its secretion.

instances, the experimental production of congenital goiter merely confirmed the views of the older students of congenital goiter in man, based on their clinical observations

A litter of four typical congenital cretins were brought to the laboratory at the age of 6 weeks, November 16, 1908. All had marked thyroid enlargement. The accompanying illustrations show the typical

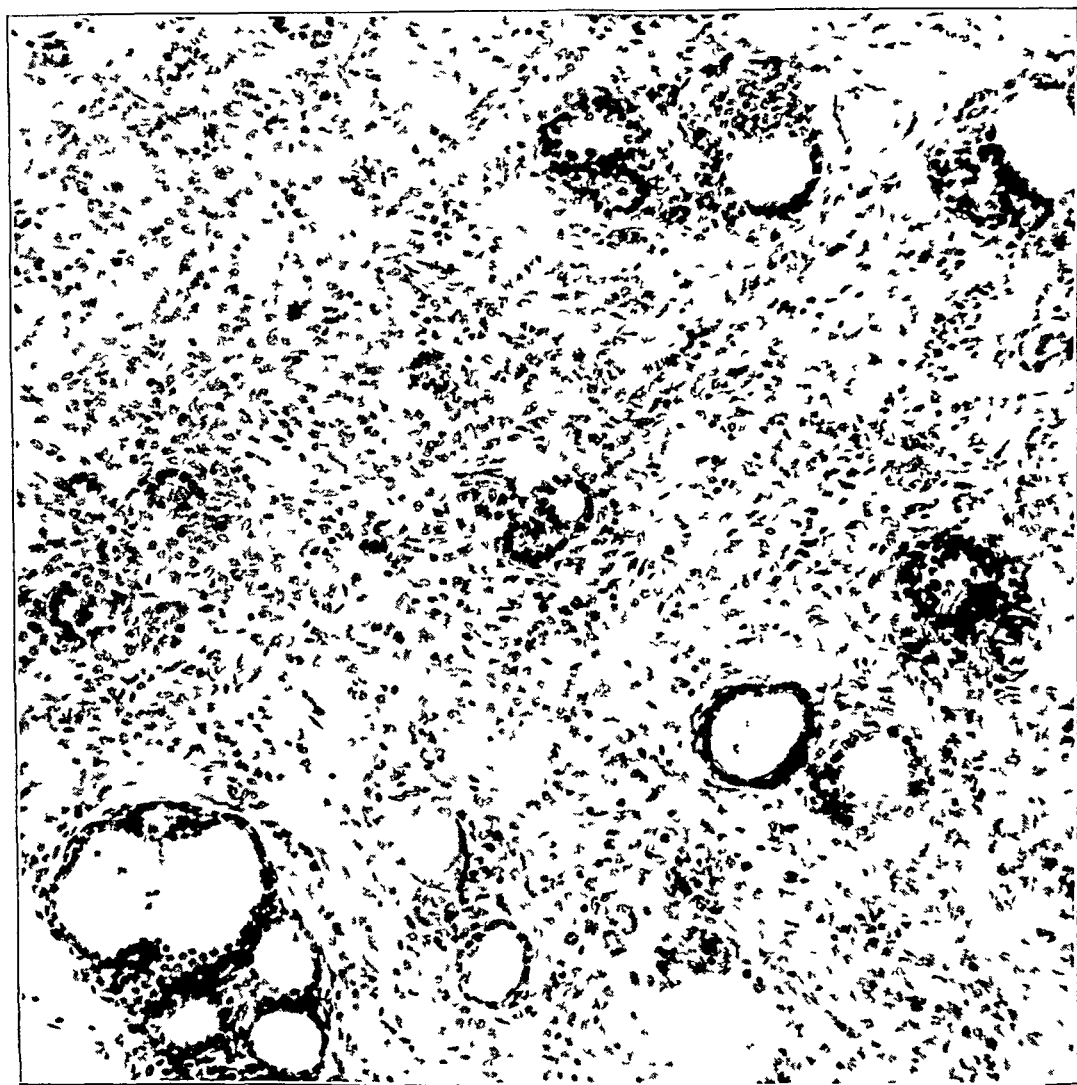


Fig 2—Section of thyroid removed Nov 25, 1908, showing high-grade myxedematous atrophy. Some of the alveoli are well preserved, others are very atrophic and undeveloped. All of the alveoli are widely separated by a soft, vascular, markedly hypertrophied stroma.

appearance of the thyroid of one of these goiterous cretins in the late stages of exhaustion atrophy and the remarkable recovery as to the anatomic and chemical condition of the thyroid following the administration of a few milligrams of iodine daily over a period of two months the puppy developed into a normal dog.

## DISEASES OF THE THYROID

If we omit anomalies of development, inflammations and tumors, the specific diseases in which the thyroid gland is known to play an important rôle may be divided into two groups

## 1 Thyroid insufficiencies

(a) Simple goiter (endemic, epidemic and sporadic)

(b) Myxedema (1) Infantile (cretinism)

(2) Adult (Gull's disease)

## 2 Exophthalmic goiter

These groups overlap to some extent. Myxedema may supervene in exophthalmic goiter and exophthalmic goiter may develop on the basis of simple goiter.

## THYROID INSUFFICIENCIES

From the standpoint of clinical medicine, simple goiter and myxedema are treated separately, but from the standpoint of physiology and pathology they are different stages of the same process. This fact was most clearly expressed by Morel in 1864: "*Le goitre est le première étape sur le chemin qui conduit du cretinisme*".

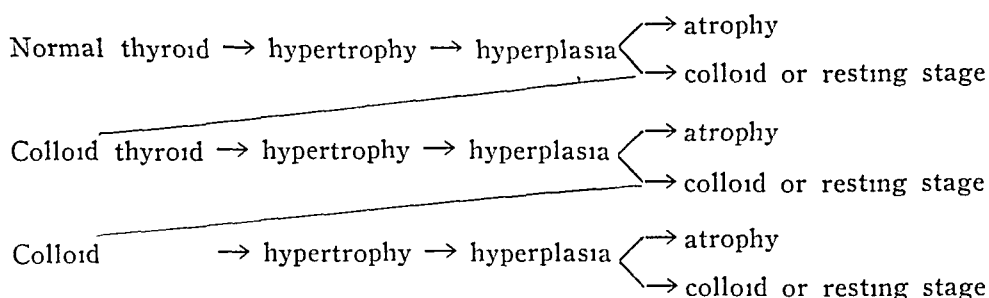
(a) *Simple Goiter*—Simple goiter is a compensatory or work hyperplasia of the thyroid gland developing during the course of certain metabolic disturbances of unknown nature, but immediately depending on a relative or absolute deficiency of iodine. It may occur endemically or sporadically in all land and fresh water animals with the ductless thyroid. Animals living in or near the sea are relatively free from goiter. In certain parts of the world—the so-called endemic goiter districts—the incidence of goiter is greatly increased. Pittsburgh lies near the southern border of the most important district of endemic goiter in North America, the center of which is in the Great Lakes basin and the St. Lawrence River Valley.

The sudden occurrence of large numbers of goiters in man and animals has been observed—the so-called epidemics of goiter. These outbreaks have been observed in troops stationed in goiterous districts, also in fish hatcheries, on poultry farms and in dairy herds.

*Etiology* The essential cause of simple goiter is unknown. The immediate cause is a relative or absolute deficiency in the iodine store of the thyroid. Goiter is, therefore, only the local sign or effect of a specific deficiency disease and may result from (1) an increase in the needs of the organism for the iodine containing hormone, as during puberty, pregnancy and lactation, during the menopause, during certain infections and intoxications, following sufficient injury to the interrenal gland (adrenal cortex) or as a result of diets consisting mainly of fat and protein, (2) interference with the absorption and utilization of the normal intake of iodine, or (3) actual deprivation of

*The Anatomic Cycle in Goiter* —As already pointed out, the thyroid is a labile tissue, capable of marked hyperplasia and involution in response to variations in functional activity. On this account, a wide range and great variety of progressive, regressive, degenerative, inflammatory, atrophic and neoplastic changes may be present, many of which, as Virchow long ago pointed out, are only terminal metamorphoses and complications occurring in long-standing goiters. These secondary changes are usually present in human goiter and have caused most of the confusion and difficulties in interpretation.

The primary or basic anatomic changes in the thyroid in goiter are relatively simple. In working with large series of goiterous and non-goiterous thyroids in fish, birds, dogs, cats, sheep, cattle, pigs and rats, we have found that the cycle of essential cell changes may be reduced to a simple schema



This cycle is the same for all animals examined, including man. The thyroid cell begins to hypertrophy when the iodine store falls below a given level, and continues this hypertrophy and hyperplasia until exhaustion; atrophy or recovery supervenes. By recovery, one means the return to the colloid or resting stage, and not, as some have supposed, the disappearance of the thyroid enlargement. The colloid gland is the condition nearest to normal, both anatomically and chemically, that a gland can assume which has once been in the state of active hyperplasia, and such colloid glands are capable of all the reactions of a normal gland. They can repeat the cycle of hypertrophy, hyperplasia and involution many times, as has been shown experimentally in dogs by producing compensatory hyperplasia, by partial removal of the colloid gland, involuting this hyperplasia with iodine, again producing compensatory hyperplasia by partial removal and again involuting with iodine. We have succeeded by this method in causing the gland to repeat its cell cycle as many as seven times in the same animal. These cell changes are not specific for any clinical disease, as some have supposed, but occur in response to any stimulus for increased thyroid activity. This stimulus may be a relative or absolute lack of iodine, the increased needs of the animal for thyroid activity during infectious diseases, during pregnancy and lactation, the result of diets high in fats and protein, as shown by McCarrison.

stances has been put forward as causal agents, but none of these has been shown to have any relationship. At present the best conception of the etiology of simple goiter is that it is a compensatory or work hyperplasia immediately dependent on a relative or absolute deficiency of iodine. Whether the deficiency in iodine is primary or secondary cannot be stated at present. When one recalls that 50 mg of iodine will maintain the thyroid in a normal state for as long as a year, and that diets rich in fat can quickly exhaust the iodine of the thyroid, it would appear that the iodine deficiency might be considered as the primary, and possibly the essential, cause. Nevertheless, we must still consider the possibility of endemic goiter being due to some chemical agent or toxin acting to divert the normal iodine intake or to increase the needs of the organism for thyroid activity.

**Pathology** The first change in the thyroid in developing goiter is a marked decrease in the iodine store. When this store has fallen below 0.1 per cent, increased vascularity, cell hypertrophy and hyperplasia occur. In the lower animals, with the exception of the rat, this cellular hyperplasia is regular and uniform, while in man it is frequently irregular and nodular—struma nodosa or adenomatous goiter. These nodules or adenomas are believed to be due to different rates of growth of cell rests of different physiologic age. These nodules are an integral part of simple goiter in man. The more differentiated types are functionally active and react with iodine, while the less differentiated fetal adenomas have lost more or less completely this characteristic. Adenomas are of great importance in clinical medicine because they are so frequently the seat of hemorrhage, cyst formation, calcification and, most important of all, they form the basis of perhaps 90 per cent of thyroid carcinomas.

**Treatment** The therapy of simple goiter may be divided into two parts: (1) prevention and (2) curative treatment.

**Prevention** Goiter is the easiest and simplest of all known diseases to prevent both in man and in animals. Apart from the experimental prevention mentioned earlier in this paper, iodine was first used in the prevention of goiter on a large scale in 1910, when it was demonstrated that this element added to water in concentrations not greater than 1:1,000,000 prevented the disease in brook trout. Since that time, iodine in some form has been successfully used commercially in the prevention of goiter in cattle, sheep, hogs and poultry. Iodine is effective when administered in any form or manner. This fact introduces difficulties and advantages, difficulties as to the selection of the best form and manner of administration, and advantages in that the desired result may be accomplished with certainty in a variety of ways. The ideal plan of administration of iodine for goiter prevention is still to be worked out. In private practice, from 15 to 30 c.c. of



iodin, either natural or experimental. Drinking water has been associated with the etiology from the remotest times and by all people, but we are still ignorant of the nature of the association. Foodstuffs grown in goiter districts and the water in such regions have been found to

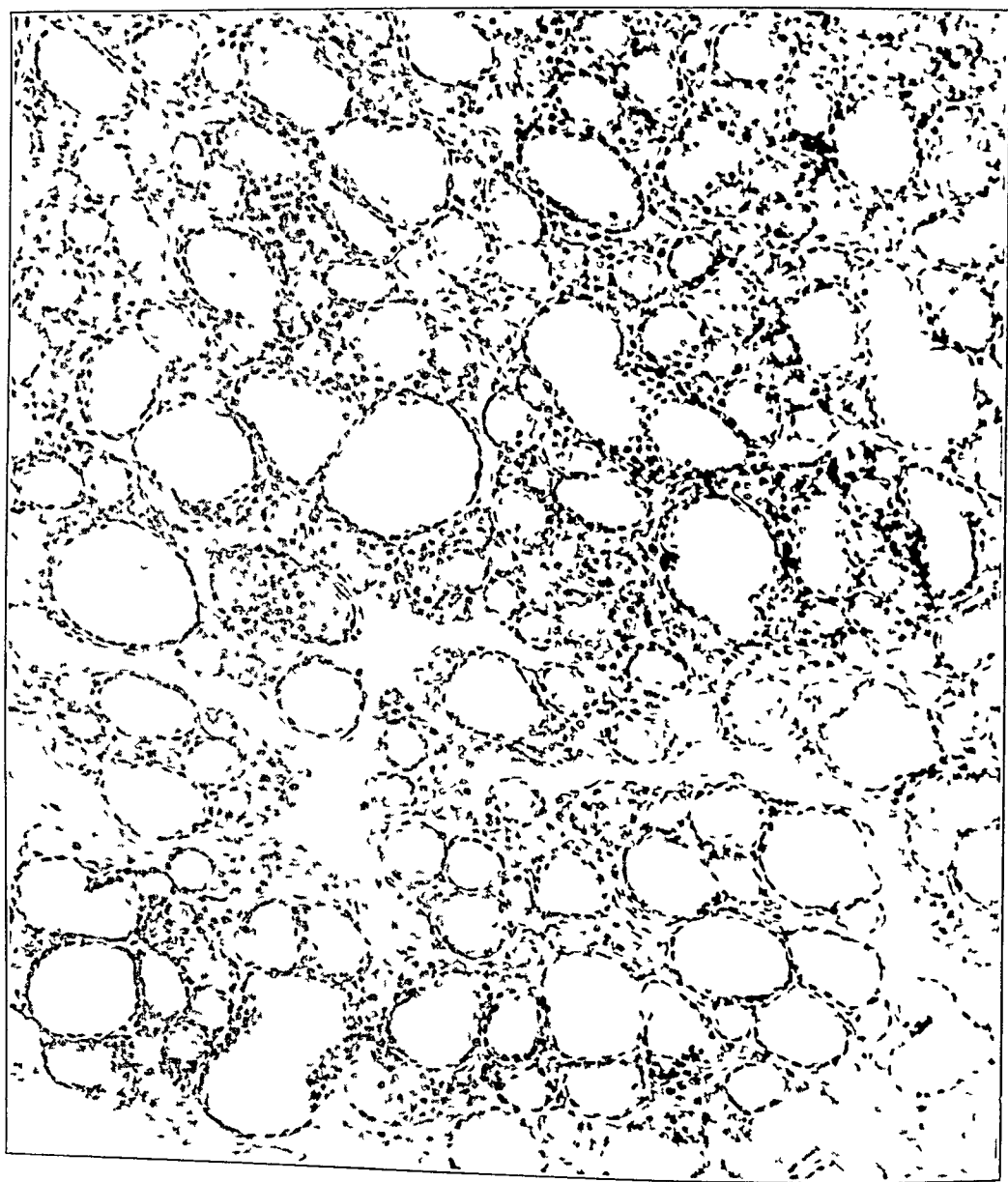


Fig 4—Section of the same thyroid removed Jan 18, 1909, showing further absorption of the stroma and nearly complete differentiation of the thyroid alveoli. The epithelium and the colloid of the alveoli are normal.

contain less iodin than in nongoiterous districts. The theory that goiter is a water-born infection is without supporting evidence. That toxins of bacterial and other origin may indirectly excite the thyroid to enlargement is well known. A great variety of chemical sub-

(b) *Myxedema*—This is a chronic disease due to a high-grade thyroid insufficiency and characterized by greatly reduced metabolism resulting in stunted mental and physical development if occurring during the growing period and in trophic disturbances, cachexia and mental deterioration if occurring in adults. Clinically, the disease may be arbitrarily divided into two groups, depending on whether it develops before or after puberty: (1) congenital and infantile myxedema and (2) adult myxedema or Gull's disease.

**Congenital Myxedema or Cretinism** The disease occurs sporadically and endemically. The sporadic form is rare and may occur anywhere, but the endemic form is associated with endemic goiter. Goiter is the first evidence of a functional insufficiency of the thyroid, and myxedema is the end stage of the severest form of this insufficiency. Many observers believe that cretinism is a more complex nutritional disturbance than can be accounted for on the basis of thyroid insufficiency. This belief is based on the facts that many other conditions—dwarfism, rickets and Mongolian idiocy—have in the past been confused with cretinism and that postnatal treatment with desiccated thyroid is usually only partially successful, while in the myxedema of adults, treatment with desiccated thyroid is highly successful. The postnatal therapeutic test is not a physiologic test for the reason that the greatest effects of thyroid insufficiency occur during fetal and early postnatal life. A more appropriate test would be to administer desiccated thyroid or iodine to the mother during pregnancy. The question is raised because of the ease with which congenital myxedema in animals may be controlled by the administration of iodine or desiccated thyroid during pregnancy or during the first weeks after birth.

All the experimental work indicates that the primary and essential lesions in cretinism may be directly ascribed to thyroid insufficiency. A loss of thyroid function sufficient to cause recognizable myxedema may have varied etiology. Injury or destruction of the gland by infection or trauma, congenital absence or smallness of the thyroid anlage, or atrophy of unknown nature are the most common causes of sporadic infantile myxedema, while endemic goiter is the most important additional factor in endemic myxedema.

**Pathologic Physiology** The essential physiologic fault is a deficiency of the iodine-containing hormone. In surviving cretins the loss is rarely complete, as in the severest form both animals and man die soon after birth. Although cretinism may occur in the first generation of goiterous parents, it is usually the summation of several generations of goiterous progenitors.

**Treatment** Prevention offers the only certain means of controlling the disease both in man and animals. The postnatal treatment is only partially successful because too much damage has been done before

syrup of hydriodic acid, given in from 0.5 to 1 c.c. doses daily and repeated each spring and autumn, is sufficient.

In the endemic goiter districts of America, 90 per cent of simple goiter could be eliminated by protecting the mother and fetus during pregnancy, and the child between the ages of 10 and 17 years. The public schools offer almost ideal conditions for carrying out goiter prophylaxis in children, and maternal and fetal thyroid enlargement could be controlled by private physicians and prenatal clinics.

In a demonstration of goiter prevention in school children, Marine and Kimball administered 2 gm of sodium iodid each spring and autumn for three years. The 2 gm was given in 0.3 gm doses daily. Of 2,190 pupils who took the 2 gm as directed, only five developed thyroid enlargement, while of 2,305 who did not take the iodid, 495 developed goiter. These amounts of iodine are excessive, 0.5 gm of sodium iodid would be as effective. In Switzerland, where the incidence of goiter is much higher, they have used iodostatin tablets containing from 1 to 5 mg of iodine. A tablet is given once a week. If the entire population is to be protected, iodized table salt is perhaps the most practical method. Sea salt, if used exclusively, or a salt containing 0.2 per cent iodine, if restricted to table use, would seem ample.

The mother and fetus may be protected against thyroid enlargement by the administration of 30 c.c. of syrup of hydriodic acid, or of an equivalent amount of iodine in any other available form extending over a month during the first half of pregnancy. Desiccated thyroid is theoretically a more direct prophylactic agent than iodine, but practically it is too dangerous a drug to be recommended for this purpose. The dangers from iodine administration in the doses recommended are negligible.

**Curative Treatment** In long-standing goiters, no plan of medical treatment is very satisfactory. In the early developmental stages of goiter, the curative effects of iodine in the doses recommended are most striking and bring about complete relief in the majority of cases if not complicated by adenomas, hemorrhage, cyst formation or other pathologic conditions. Perhaps the most satisfactory plan of medical treatment is to administer from 2 to 4 gm of desiccated thyroid in 0.2 gm doses daily, and after allowing an interval of two weeks without treatment, to saturate the thyroid with iodine by giving 30 c.c. of syrup of hydriodic acid or its equivalent in iodine in from 1 to 2 c.c. doses daily. This treatment may be repeated every third or sixth month. The maximum reduction will occur in from six to twelve months. As a general rule, neither iodine nor desiccated thyroid should be given when exophthalmic goiter is suspected, although there are certain stages of this disease that are materially benefited by the administration of iodine in milligram doses.

glands, suprarenal (adrenal medulla) and interrenal glands (adrenal cortex) are also involved in an important way \*

It was in the hope of finding additional facts regarding thyroid interrelations, and possibly some new data relative to exophthalmic goiter, that I undertook an investigation of the thyroid sex-gland interrelations. The thyroid sex-gland interrelationship is perhaps one of the longest known and most striking examples of interrelations of glands with internal secretion. Thyroid enlargement is intimately associated with the cyclic activities of the sex glands, and it occurred to us that since the adrenal cortex is in many ways closely related to the sex glands, further data on the sex-gland-thyroid interrelationship might be obtained by studying the effects of cortical injury on thyroid function. I have used heat production as the best available method for measuring variations in thyroid activity. Golyakowski, in 1899, first observed the increased heat production which follows severe but sublethal injury to the adrenals in the dog.

In collaboration with Drs. Baumann and Scott, I have studied the heat production in a large series of rabbits and cats following adrenal injury. In rabbits we have produced adrenal insufficiency by removal of the glands and by freezing the cortex after mobilization with as little injury to the blood and nerve supply as possible. In cats, we have in addition utilized the method of vein ligation. The reactions as to heat production following these forms of injuring the adrenal function may be divided into three groups: (1) those that survive indefinitely with no appreciable alterations in heat production, (2) those that show an increase in heat production, and (3) those that show a fall in heat production. Of thirty-three rabbits in which both adrenals were removed, twenty-seven, or 82 per cent, showed a rise in heat production varying from 10 to 63 per cent. The rise is absolute and usually begins in from three to six days after removal or injury of the adrenals and lasts from a few days to several months. Sometimes in rabbits, and frequently in cats, the rise in heat production is preceded by a fall lasting two or three days.

Infection, trauma and nerve injury, it is believed, may be eliminated as important factors in this increased heat production. The simplest explanation for the increased heat production with the facts at present available, is that it is in part due to increased thyroid activity brought about by the removal of the regulatory and inhibitory influence normally exercised by the adrenals, and that it is dependent on cortical rather than on medullary function. In order to determine whether the thyroid

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\* On account of the dual nature of the suprarenal gland the terminology of comparative anatomy has been adopted, namely, "adrenal gland" includes both the medulla and cortex, "suprarenal gland" includes only the medulla or chromophil tissue and the "interrenal gland" includes only cortical tissue.

treatment can be instituted. Remarkable cures may be obtained in cretin animals when treatment can be started shortly after birth. Since all the available evidence indicates that endemic cretinism is due to the same physiologic fault as endemic goiter, and since congenital myxedema may be readily controlled in animals by the administration of iodine to the mother during pregnancy, I believe that the elimination of endemic cretinism is as simple as the elimination of endemic goiter, and can be accomplished by the same means. To this end it is necessary to see that the mother obtains 2 to 5 mg of iodine weekly in some available form during pregnancy and that this be continued from time to time during the growing period of the child. Just as in the prevention of endemic goiter, the most practical means of prevention will probably be the state-wide use of salt containing from 1 to 2 mg of iodine per gram.

**Myxedema of Adults (Gull's Disease)** This is the best understood effect of a pathologic decrease in thyroid function, because it is not complicated by the ill-understood and intricate chemical processes of growth and development. Spontaneous and operative or experimental myxedema are essentially identical. The first experimental myxedemas, reported in 1882 and 1883, were produced in man by the Reverdin brothers and by Kocher by the removal of goiters. Spontaneous myxedema is from six to eight times more common in women than in men, and exophthalmic goiter is the most important antecedent. The disease, as pointed out by Gull, is usually associated with exhaustion atrophy of the thyroid, but occasionally thyroid enlargement may be present. In endemic myxedema, thyroid enlargement is the rule. As regards treatment, in the rare instances in which there is abundant active thyroid, iodine is as efficacious as desiccated thyroid, just as in congenital myxedema. In all other cases, the iodine-containing hormone must be supplied—best in the form of desiccated thyroid. The treatment of myxedema by thyroid, discovered by Murray in 1891, is one of the triumphs of applied physiology.

#### EXOPHTHALMIC GOITER

While studies in pathology and physiology have as yet contributed very little toward clearing up the nature of this obscure disease, they have indicated that the most suggestive lead lies in the field of the interrelations of glands of internal secretion. Exophthalmic goiter may be defined as the manifestation of a disturbance of the regulatory control and functional interactions of organ activities, characterized by increased metabolism of thyroid origin, asthenia and tachycardia. The thyroid plays an important rôle in the clinical manifestations of the disease, but we must look beyond this gland for the essential and primary lesions. So, also, there is evidence that the thymus, liver, sex

third day from birth to the thirty-fifth day of life. A sharp rise in heat production was observed during the second week of extra-uterine life, coinciding with the onset of the cortical destruction. Our figures were as given in the table.

*Rise in Heat Production After Birth*

	Calories per kg per hour
From 1 to 7 days	1.88
From 8 to 14 days	2.14
From 15 to 21 days	2.15
From 22 to 28 days	2.30
From 29 to 34 days	2.34

The rise during the second week was much greater than the combined rise during the next three weeks of observation. A rise in heat production follows both the normally occurring and the experimentally produced injuries to the interrenal gland, provided the thyroid gland is intact, but it does not occur in animals when the thyroid gland has been previously removed. If the interrenal gland directly or indirectly exercises a restraining or regulatory control over the thyroid gland, it may be found to have an important relation to the etiology of exophthalmic goiter. In studying the clinical manifestations of chronic sublethal interrenal insufficiency in cats and rabbits, one is impressed by the points of similarity between it and some of the outstanding features of exophthalmic goiter. The most prominent single feature in each is a significant increase in heat production. Each condition has a phase of increased fatigability, asthenia and exhaustion. In both conditions, there is evidence of myocardial injury. Diarrhea, increased or decreased appetite, nutritional and weight changes, are present in both. A rapid loss of iodine associated with thyroid hypertrophy is also present in each. Finally, that rather rare form of exophthalmic goiter, running a fatal course in a few weeks, with marked asthenia, tachycardia, hyperthermia and coma, bears a striking resemblance to the effect produced by experimental interrenal insufficiencies terminating fatally in one or two weeks.

was a factor in the increased heat production, fifteen experiments were carried out. After control heat production measurements had been made over a period of from two to three weeks, the thyroid glands were removed and the metabolism allowed to fall to its lowest level, usually in about three weeks, and then the adrenals were removed either in one or two sittings and heat production measurements continued until the animal died or until further observations seemed unnecessary. In only two instances after adrenalectomy were there significant rises in heat production above the level obtaining after thyroidectomy, but in no instance did the heat production rise to the normal level.

The striking feature of these experiments is the absence of a significant rise in thirteen of fifteen rabbits in which adrenalectomy was performed after thyroidectomy, in comparison with a rise of more than 10 per cent in twenty-seven of thirty-three rabbits with intact thyroids, in which the adrenals were removed. Further, there is evidence that the iodine store in the thyroid is markedly reduced during the period of increased heat production following injury to the adrenals, and, in addition, we have been able to cause secondary rises in heat production after thyroid exhaustion by the administration of a few milligrams of iodine. These facts, we believe, establish another thyroid-adrenal interrelationship which, with our present knowledge, seems to depend on an antagonistic action of the thyroid and interrenal gland (adrenal cortex). The fact that increased heat production occurs after removal of most of the chromophil tissue, indicates that epinephrin has very little to do with it. It is possible that, if increased epinephrin discharge could be combined with interrenal insufficiency, a much greater rise in heat production could be brought about. It should be pointed out that while the thyroid-interrenal gland interrelationship appears to be an important one, it is only one of many functions in which the interrenal gland is directly or indirectly concerned.

In this connection, it is appropriate to refer to some measurements of heat production in infants during the normal involution of the adrenal gland, which begins during the second week of extra-uterine life. This involution is a remarkable destruction of the two inner layers of the cortex. It begins as a hemorrhagic infiltration, going on to necrosis and finally to absorption of these layers, with a folding and collapse of the glomerular zone on to the medulla. While the physiologic significance of this normal destruction of the cortex in human infants' adrenals is unknown, it occurred to us that it might be in effect a naturally occurring cortical injury bringing about an alteration in heat production similar to that found in animals following experimental sublethal destruction of the cortex. Lowe and Cipra and I studied the heat production in ten normal infants every second or

and others working with or under the direction of Rosenow have reported similar results. The greater number of workers have, however, failed to obtain evidence of an elective localization. Thus Moody<sup>10</sup> found no evidence of a tendency to specific localization in the injection of bacteria from chronic dental foci. Henrici,<sup>11</sup> in studying the specificity of streptococci, could demonstrate no tendency of the organism to reproduce the disease from which the patient suffered. Meyer<sup>12</sup> suspects the selective action of bacteria, and considers that it is the tissues of the animal which determine the local lesion.

Few of those who have attempted to verify Rosenow's work have given the proper consideration to certain fundamental technical details. The bacteria employed in animal inoculations have often been subcultivated aerobically. Rosenow has emphasized that the bacteria concerned in chronic foci are very sensitive to oxygen, and that the property on which elective localization depends tends to disappear promptly on aerobic cultivation. To demonstrate an elective localizing power the culture medium must be favorable with regard to oxygen tension, and the animal inoculations must be made with freshly isolated cultures. The necessity for providing the proper oxygen tension in the culture medium cannot be emphasized too strongly. There is much to suggest that an adaptation to a certain oxygen tension is largely the determining factor in elective localization. It has been well stated<sup>13</sup> that "a focus is of importance not only as affording an entrance way for bacteria but also as a place where varying affinities may be acquired."

It is important to decide, if possible, whether bacteria do have a selective affinity. Certainly the best experimental proof we have of the etiologic relationship of a focus of infection to a certain lesion is the reproduction of the lesion in animals by the injections of bacteria isolated from a focus in the patient. It is still better proof of an etiologic relation if it is shown that the reproduction of the lesion is dependent on the specific tendency of the bacteria to produce the lesion which the organism causing the patient's infection is evidently producing.

Certain considerations in a study of elective localization should be emphasized. Some lesions are exceedingly easy to produce in animals. Thus joint involvement is commonly found after the intravenous injection

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# ELECTIVE LOCALIZATION IN THE EYE OF BACTERIA FROM INFECTED TEETH\*

RUSSELL L HADEN, M A, M D

KANSAS CITY, MO

An etiologic relationship between chronic foci of infection and systemic disease is accepted by most clinicians. The cure or marked improvement in some systemic disorder which may follow the removal of a septic focus seems conclusive proof of a causal relation. The clinical manifestations of focal infection depend primarily on the site of localization of the bacteria which are fed into the blood stream. The extent of clumping of the organism, the nature of the blood supply, the food supply and local tissue resistance must play important parts in determining the localization and resulting infection.

Rosenow<sup>1</sup> has emphasized also the individual variation in bacteria and has advanced the theory that bacteria have a specific tendency to localize in certain tissues of the body, dependent on some peculiar inherent property. The theory is a most attractive one and has evoked a great deal of discussion. If it is true that bacteria have peculiar localizing or infecting powers, many obscure phenomena of disease are explained. The theory concerns especially the streptococci commonly associated with chronic disease of bacterial origin. Rosenow has demonstrated that such streptococci freshly isolated from infected tissues and from foci of infection in patients suffering from rheumatic fever,<sup>2</sup> erythema nodosum,<sup>3</sup> ulcer of the stomach, cholecystitis, herpes zoster, myositis,<sup>4</sup> appendicitis and epidemic parotitis,<sup>5</sup> and acute poliomyelitis,<sup>6</sup> tend to reproduce in animals the lesion from which the patient suffered. Bumpus and Meisser,<sup>7</sup> Meisser and Gardner,<sup>8</sup> Hardt<sup>9</sup>

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7 Bumpus, H C, and Meisser, J G. Foci of Infection in Cases of Pyelonephritis, *J A M A* **77** 1475 (Nov 5) 1921

8 Meisser, J G, and Gardner B S. Elective Localization of Bacteria Isolated from Infected Teeth, *J Nat Dent Assn* **9** 578 1922

9 Hardt, L L J. The Secretion of Gastric Juice in Cases of Gastric and Duodenal Ulcer, *Am J Physiol* **40** 314, 1916

was responsible for 139 of 215 cases reported by him. De Schweinitz<sup>18</sup> aptly sums up the question in the statement that there is "no better established etiological relationship than that between septic foci in dental areas and certain diseases of the eye, especially those of the uveal tract." Such conclusions are based largely on the clinical improvement noted after the eradication of foci of infection.

There is little experimental proof, however, of a relation between focal infection and eye disorders. Irons, Brown, and Nadler<sup>19</sup> studied a streptococcus isolated from the infected tissues of a patient suffering from dacryocystitis and iritis. They found that a large percentage of rabbits developed eye lesions when injected intravenously with the freshly isolated culture. The ability to produce specific lesions was lost on subculture and on passage. The loss of specific tendency to localize in the eye was not accompanied by any demonstrable decrease in virulence for rabbits. Rosenow<sup>20</sup> has reported cases of eye infection from a dental pulpitis with the reproduction of the lesion in animals. Meisser and Gardner<sup>8</sup> have reported a similar case.

#### METHODS

In making the bacteriologic studies of tooth infections I have followed closely the methods of Rosenow.<sup>4</sup> All cultures have been made in glucose brain broth and glucose brain agar. The mediums are prepared according to Rosenow's directions.

**Glucose Brain Broth** dehydrated bacto nutrient broth, 8 gm, sodium chlorid, 8 gm, dextrose, chemically pure, 2 gm, Andrade indicator, 10 cc, and distilled water, 1,000 cc. The broth and salt are dissolved by heating. After cooling, the indicator and dextrose are added. The medium is tubed in 6 by three-fourths inch test tubes so that the depth is at least 3½ by 4 inches. Three pieces of calf brain, about 1 cm square, and two or three pieces of crushed marble are added to each tube. The tubes are then sterilized for twenty minutes in the autoclave at 20 pounds' (907 kg) pressure.

**Glucose Brain Agar** The agar medium is made by adding 7 gm of powdered agar to 1 liter of the glucose brain broth prepared as indicated above. The calf brain and marble are then added, and the medium is sterilized.

The brain substance renders the bottom of the medium anaerobic, the top is aerobic, so that every degree of oxygen tension between these two points is provided. The nutritive qualities of these mediums are especially favorable for the growth of the organisms encountered in infections about the teeth. The agar medium we have found especially valuable in showing the relative number of bacteria present in the material inoculated. It will barely solidify but is hard enough to hold colonies discrete without restraining growth. The appearance of a brain agar tube is shown in Figure 1.

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18 De Schweinitz, George E. Dental Sepsis in Its Relation to Ocular Disorders, *Dental Cosmos* **42** 565, 1920.

19 Irons, E. E., Brown, E. V. L., and Nadler, W. H. The Localization of Streptococci in the Eye. A Study of Experimental Iridocyclitis in Rabbits, *J. Infect. Dis.* **18** 315, 1916.

20 Rosenow, E. C. Focal Infection as a Cause of Iritis, *Med. Clin. N. America* **5** 573, 1921.

tion of many different types of bacteria. The production of arthritis in an animal with the bacteria isolated from an infection in a patient suffering from arthritis in a single instance, is little proof of a causal relation and still less of elective localization. The only data of value are those showing that the bacteria from a large group of persons with arthritis produce arthritis in a much higher percentage of animals than those from a similar number of persons not suffering from arthritis.

The lesions which are especially desirable for a study of elective localization are those which occur rarely on routine intravenous injection. We have recently been observing the lesions produced in animals by the intravenous injection of bacteria isolated from chronic periapical dental infection. During this time we have had the opportunity of noting the lesions produced by streptococci isolated from dental areas of infection in a group of patients suffering from infections of the eye. The results seem to offer some data of value in determining the truth of the theory of elective localization and the relationship of the infection to the diseased process.

Eye infection occurring in animals after intravenous injection may be a part of the widespread lesions of a septicemia, associated with an infection of the central nervous system, or a specific localization in the eye. Involvement of the eye is seen only in a small proportion of animals on routine injection. Rosenow<sup>13</sup> found eye infections in thirty-two of 833 animals injected with cultures from varying sources. Moody<sup>10</sup> obtained eye infections in 17 per cent of 178 animals injected with bacteria from dental foci. The accessibility of lesions of the eye to direct observation and ophthalmoscopic examination is also a great advantage in such an experimental study.

A close clinical relationship between oral sepsis and infections of the uveal tract has long been recognized. Black,<sup>14</sup> in summarizing the literature concerning ocular disease resulting from dental lesions, cites clinical reports bearing on this relation which were published as early as 1842. Butler,<sup>15</sup> in a study of 100 cases of infection of the uveal tract, decided that 12 per cent were definitely due to oral sepsis. He considered that the etiology of 41 per cent was doubtful, but concluded that probably a large part of these originated in oral sepsis. B. T. Lang<sup>16</sup> classified 71 out of 176 cases of eye infection as due to septic foci about the teeth. William Lang<sup>17</sup> thought that pyorrhea

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14 Black, A. D. Ocular Disorders Resulting from Dental Lesions, *Ophth Rec* 24 1915, 1915

15 Butler, T. H. Etiology of Iritis, *Brit M J* 1 804 (April 8) 1911

16 Lang, B. T. Influence of Septic Infection in the Causation of Eye Disease, *Brit M J*, Feb 22 1913

17 Lang, William. Influence of Chronic Sepsis on Eye Disease, *Lancet* May 17, 1913 p 1368

twenty-four hours. When cultures were taken from several teeth from one patient, the several broth cultures were often mixed before injection. The rabbits varied somewhat in size but averaged about 1,500 gm. Each animal was given 5 c.c. of the broth suspension.

The animals have been watched carefully for eye lesions. Usually necropsy was performed on one animal from each culture three days after the injection, and on the second six days after injection. Occasionally animals have been kept for longer periods for observation. One animal has been observed for nine months. At necropsy the animals were carefully examined for lesions. No lesions were considered as present unless plainly visible to the naked eye. Microscopic sections have been made of many of the tissues. Cultures have often been made of the organs at necropsy, but not in a routine manner.

The patients studied have all suffered from eye infections which were considered as blood-borne and possible manifestations of focal infection. Patients with a positive Wassermann test have all been excluded except one (Case 5), which was included before the Wassermann report was received. A complete physical examination was made in all cases but one. The tonsils had not been removed from some patients, and could not be excluded as an additional factor. No apparent foci except the teeth and tonsils were found.

#### EXPERIMENTAL OBSERVATIONS

Positive cultures were obtained from the root tip or pulp of one or more teeth of fifteen patients suffering from metastatic eye infections. Staphylococci and streptococci were the only organisms recovered. Streptococci were found almost constantly as the predominant organism. Staphylococci were occasionally observed in pure culture but were usually present only in small numbers in association with streptococci. No relation has been found between the type (Holman) of organism and the pathogenicity.

Sixty-six rabbits have been injected intravenously with the bacteria isolated (Group 1). At least two rabbits were injected with the single culture or the mixed cultures from a patient. Two animals were used for the culture from each tooth found infected in several patients. Forty-five, or 68.2 per cent, of the sixty-six rabbits developed eye lesions. The positive findings include one or more rabbits from fourteen patients. The one patient whose cultures produced no syphilitic lesions was found later to have a positive Wassermann test.

As a control on these results we have the result of the inoculation of 169 rabbits by the same uniform technic with the cultures from the teeth of patients who were suffering from no systemic disease or from systemic disease other than infection of the eye (Group 2). Of this group, twenty-five, or 14.8 per cent, had lesions in the eye, twelve, or nearly 50 per cent, of these were associated with meningitis, the majority of the remaining thirteen were a part of an evident septicemia with generalized lesions. Only six, or 13 per cent, of the lesions in Group 1 were associated with meningitis, and few animals showed evidences of a septicemia.

In making cultures of tooth infections the greatest care is necessary to avoid surface contamination. We have found that sterile cultures can be quite uniformly obtained from the tips of anterior vital teeth by the procedure which we have employed. It is apparent that unless sterile cultures can be obtained from noninfected vital teeth, cultures of pulpless teeth are of little value. We have utilized the following technic. Before extraction the teeth are thoroughly scrubbed with gauze, after which the field of operation is painted with tincture of iodine. Care is taken that the iodine penetrates well into the space between the gum margin and tooth, and between the teeth. The iodine is removed with alcohol and the area of operation walled off with sterile gauze.

The tip of the extracted tooth is cut off with sterile forceps directly into a test tube containing a few cubic centimeters of sterile salt solution and a small amount of sharp sand. The tubes are well shaken to macerate the tissue on the tip of the tooth as completely as possible. The mediums are inoculated by



Fig 1—Original glucose brain agar culture tube from the tip of tooth indicated by arrow in Fig 4

pouring the salt solution containing the suspended tissue into a tube of agar which had been heated and cooled to 40 C. The tube is quickly inverted once and allowed to harden. The small amount of salt solution remaining in the tube is poured into a tube of glucose brain broth. The inoculated tubes are incubated at 37 C for from twenty-four to forty-eight hours. A smear is made from the broth culture and stained by Gram's stain. A transplant of the broth culture is made to a blood agar plate. Subcultures are made of streptococci from the blood agar to lactose, mannite and salicin fermentation tubes. According to the appearance of the colonies on blood agar and the fermentation reactions, the streptococci are classified by Holman's table<sup>21</sup>.

Rabbits have been injected intravenously with the broth culture as soon as a good growth was obtained. This was never more, and usually less, than

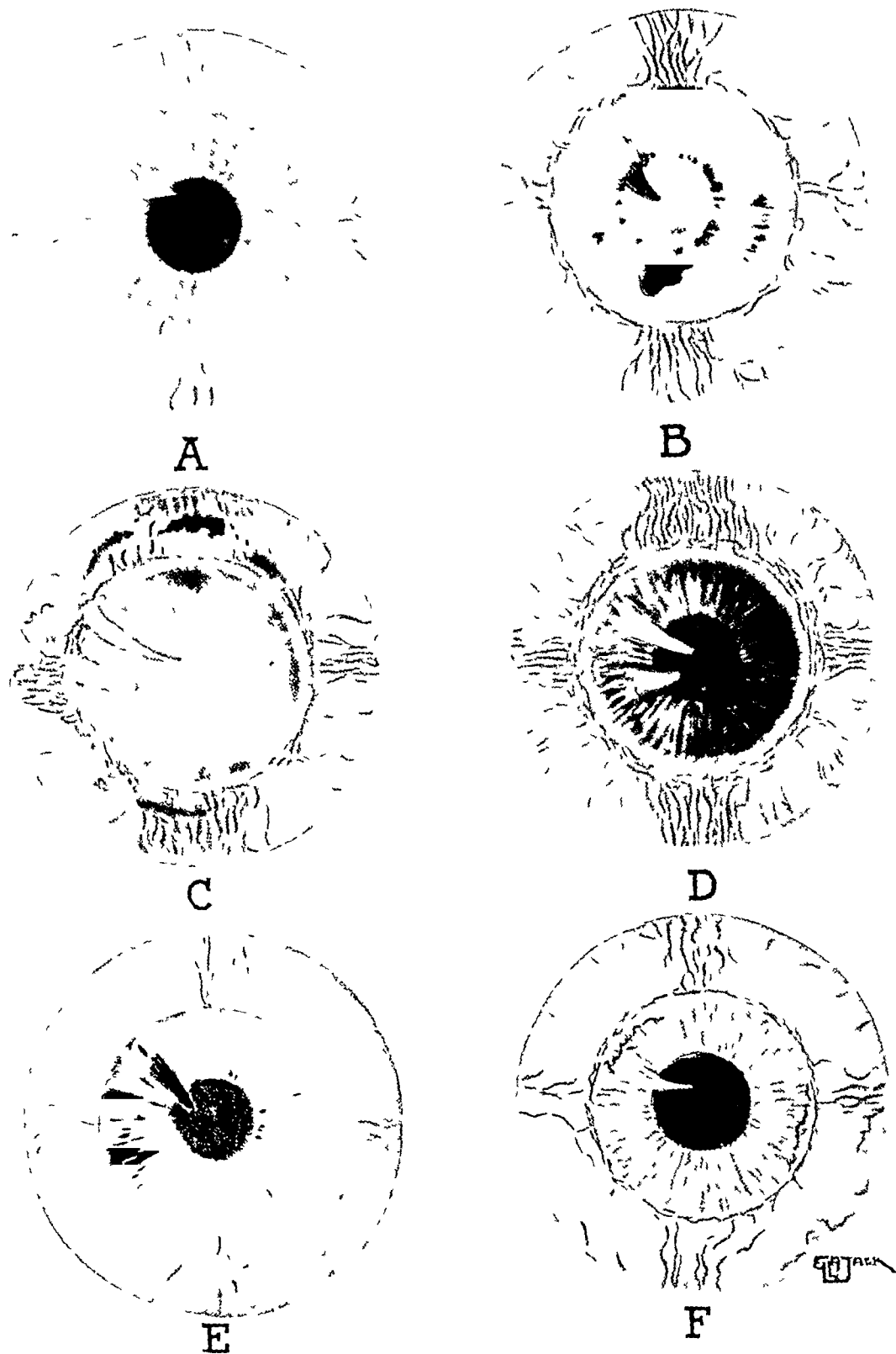


Fig 2—*a* represents the normal eye of an albino rabbit *b*, the left eye of Rabbit 4, forty-eight hours after the intravenous injection of a culture from the root tip (Fig 4) in a case of recurrent hyalitis (Case 1) Note the exudate in the anterior chamber and the circumcorneal injection *c*, eye of Rabbit 87 injected with the cultures of root tips in a case of iritis, and episcleritis (Case 10) Note the pericorneal injection, hemorrhages in iris and sclera and exudate in anterior chamber *d*, eye of Rabbit 95 injected with the mixed cultures of the root tips of the upper incisor teeth (Fig 5), in a case of recurrent iritis (Case 8) A photomicrograph of the iris and ciliary body of this eye is shown in Figure 10 *e*, right eye of Rabbit 12 eight days after the intravenous injection of the attenuated culture from the root tip (Fig 4) in a case of recurrent hyalitis (Case 1) Note the absence of light reflex due to an opacity of the vitreous humor A photomicrograph of the vitreous of this eye is shown in Figure 11 *f*, eye of Rabbit 43 six months after the injection of cultures from the root tips in a case of iridocyclitis following the removal of a congenital cataract (Case 4) This animal had recurring attacks of iritis

The percentage of lesions in the principal organs affected in the two groups are shown in the table. The incidence of joint involvement is about the same in the two groups. The muscle, kidney, heart, brain, stomach and duodenum showed a smaller percentage of lesions in Group 1 than in Group 2. Numerous animals in Group 1 showed no lesions except those of the eye. The fact that organs other than those involved in the patient are affected in the animal is taken by some as evidence against the theory of selective localization. Careful examination of patients will demonstrate, however, that few suffering from focal infection show only one manifestation of metastatic localization. The presenting lesion is usually simply the predominant one.

The most common anatomic lesion was an iritis or iridocyclitis. Some animals showed multiple hemorrhages in the iris, limbus or sclera, cloudy fluid in the anterior chamber, cloudy cornea and hyalitis. Drawings from life of typical lesions are shown in Figure 2. Pericorneal

*Localization of Bacteria Isolated from Infected Teeth \**

Group	Number of Animals	Percentage of Animals Showing Lesions in							
		Joint	Muscle	Kidney	Endo- cardium	Myocar- dium	Brain	Stomach and Duodenum	Gall bladder
1	66	65.2	22.7	39.4	10.6	4.5	10.6	68.2	1.5
2	169	66.7	35.5	48.5	13.0	10.6	12.4	14.8	10.1

\* Group 1 consists of animals injected with bacteria isolated from teeth of patients suffering from metastatic eye infection. Group 2 consists of animals injected with bacteria isolated from teeth of patients suffering from no systemic disease or from systemic disease other than eye infection.

injection often developed a few hours after the inoculation. In some animals the injection was progressive, in others it disappeared, only to reappear at a later date with an evident infection.

Histologic examination of the eyes showed injection of vessels (Fig. 9), or hemorrhage in the iris and ciliary body in some specimens. Others showed the diffuse inflammation of a panophthalmitis, including the extra-ocular muscles. Still others showed a marked cellular infiltration of the choroid (Fig. 11). One showed only an infiltration of cells in the vitreous humor (Fig. 12). Typical histologic findings are shown in Figures 9, 10, 11 and 12.

Cultures were not made according to routine from all the eyes affected, as the specimens were preserved for histologic examination. Numerous cultures have been made, however, from the iris, and aqueous or vitreous humor. Organisms were recovered from all eyes from which cultures were taken during the course of an active infection. In one instance, the organism was carried through three series of animals.

## COMMENT

The fact that 68.2 per cent of the animals injected with bacteria isolated from tooth infection in patients suffering from metastatic eye infection developed eye infections, while only 14.8 per cent of the animals inoculated with cultures from other sources showed similar lesions, could hardly be explained otherwise than by granting a selective action on the part of the bacteria. The findings thus offered confirmatory evidence of the validity of Rosenow's theory of elective localization. Our results have an added interest in that they demonstrate again experimentally the well recognized clinical relation of dental infection to ocular disease.

In a number of instances we have been able to produce specific eye lesions with bacteria isolated from the tips of teeth which seemingly showed no evidence of infection in the radiograph. We have found repeatedly that large numbers of bacteria may be grown from a root tip around which there is not enough destruction of bone to be evident in the radiograph. This needs to be emphasized because often infection around a pulpless tooth is ruled out simply because the radiograph does not show bone absorption. Such teeth are often allowed to remain in the jaw even in the presence of serious metastatic systemic disease in which the eradication of all possible foci is urgently indicated.

Some of the case histories reported below illustrate a number of the problems encountered in the management of chronic periodontal infection. Case 8 is of special interest. The complete radiographs are shown in Figure 5. The only tooth around which there is evident bone destruction is indicated by an arrow. On culture this showed a large number of colonies of a streptococcus which produced no eye lesions in rabbits. An animal inoculated with the mixed cultures from the upper incisor teeth developed the eye lesion shown in Figure 2 *d*. The patient stated that the worst attack of nitis which he had suffered occurred while the dental restorative work on the upper incisors was being done.

One patient (Case 12) had no pulpless teeth. A molar tooth (Fig. 6) which had a large filling was removed, largely because there was a pocket around it which could not be cleaned up well otherwise. The tooth had responded normally to tests for vitality, but on opening the pulp chamber under sterile precautions, the pulp was found to be swollen and hyperemic. From the pulp a pure culture of a green-producing streptococcus was obtained. The eye of a rabbit injected with the mixed cultures from the root tip and pulp is shown in Figure 7. On further questioning there seemed to be an evident connection between the infection of this tooth and the patient's first attack of nitis. Two patients (Cases 4 and 10) developed infections of the eye subsequent to an operation on the eye, such as the removal of a





A general physical examination on Feb 24, 1922, was negative. The tonsils had been removed. Blood examination revealed red cells, 4,632,000, hemoglobin, 90 per cent, white cells, 7,400. The differential count was polymorphonuclear neutrophils, 55.5 per cent, polymorphonuclear eosinophils, 4.5 per cent, polymorphonuclear basophils, 2 per cent, small mononuclears, 25.5 per cent, large mononuclears and transitionals, 12.5 per cent. The urine showed no abnormality, and the Wassermann test was negative. A roentgenogram of the teeth showed that the upper left cuspid (Fig 4), and the lower left second bicuspid were pulpless with poor canal filling and some bone absorption at the root tip. The lower left lateral incisor was a peg tooth, the root was poorly filled, and there was a large alveolar abscess. The three pulpless teeth were extracted. The brain agar cultures showed no growth from the lower left lateral incisor, and only a few colonies from the lower left second bicuspid. The culture of the upper left cuspid showed an infinity of colonies of a nonhemolytic streptococcus (Figs 1 and 3). March 1, 1922, Rabbits 3 and 4 were injected with the broth culture from the upper left cuspid. Rabbit 3 developed numerous patches of choroidoretinitis and died three weeks later. The necropsy findings were ascites and very large white kidneys. Rabbit 4 developed exudate in the

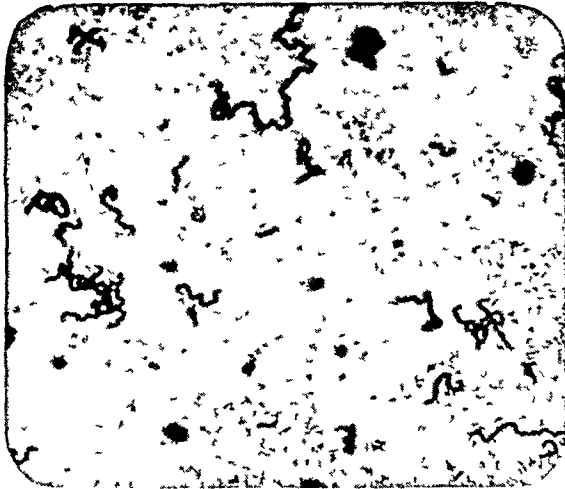


Fig 3—Photomicrograph of streptococcus from culture tube in Figure 1

anterior chamber and corneal opacities of both eyes twenty-four hours after inoculation. The following day the eyeballs were extremely red. The right iris was discolored all the way around and the left partly around (Fig 2 *b*) with a milky gray exudate. There were grayish deposits on the cornea. The animal was killed. Necropsy was negative except for the eye findings. The streptococcus was recovered by smear and culture from both eyes. On March 5, Rabbits 5 and 6 were inoculated with streptococcus recovered from the left eye of Rabbit 4. Rabbit 5 developed circumcorneal injection and a choroidoretinitis and died thirteen days later. Necropsy showed only kidney abscesses. Rabbit 6 developed a marked injection of both eyes and died within twenty-four hours. A short chain streptococcus was recovered from the eye. Two rabbits injected with this culture died in a few hours without showing any localized lesions. Rabbits 7 and 8 injected with the culture from the right eye of Rabbit 4 developed patches of choroidoretinitis and were killed six weeks later. Rabbit 7 showed a purulent arthritis. Rabbit 8 was negative.

Three weeks after the original apical cultures had been made, organisms were removed with a sterile pipet, grown in broth for twenty-four hours, and injected into Rabbits 9, 11 and 12. Rabbit 9 developed a cloudy vitreous and died four days after inoculation. Necropsy revealed an arthritis. Rabbit 11 showed a pericorneal injection which gradually cleared up. Rabbit 12 had a

cataract Here the localized diminished resistance must also have been a factor in the localization of the bacteria Two patients had iritis with arthritis Another had attacks of iritis with chronic glaucoma The case reports and protocols of animal experiments in the individual cases are reported in detail below

#### SUMMARY

A study of the eye lesions produced in rabbits by the intravenous injection of streptococci and staphylococci isolated from chronic dental infection is reported

All cultures have been made in Rosenow's glucose brain mediums to afford the proper nutritive material and the optimum oxygen tension

The animals were inoculated with freshly isolated cultures, usually the injection was made within twenty-four hours after the extraction of the tooth

Sixty-eight and two tenths per cent of sixty-six rabbits inoculated with the cultures obtained from fifteen patients suffering from metastatic eye infection developed lesions of the eye

Fourteen and eight tenths per cent of 169 rabbits inoculated with cultures from patients other than those suffering from eye disease developed lesions of the eye

The much higher percentage of animals showing lesions in the eye when inoculated with bacteria from patients suffering from ocular diseases indicates some selective affinity of the bacteria for tissues of the eye

The results offer proof of the etiologic relation of infection in dental areas to diseases of the eye

Teeth which are negative in the radiograph may bear as important an etiologic relation to disease as those which show evident infection

#### CASE REPORTS AND PROTOCOLS OF ANIMAL EXPERIMENTS

CASE 1—*Recurrent hyalitis* L P, a steamfitter, aged 25, was first seen, June 25, 1920 He complained of seeing something flying around in front of the right eye This was first noticed about three weeks before following an attack of influenza It was gradually becoming worse

The fundus was seen with difficulty, but no hemorrhages were present Many fine dustlike opacities and some larger ones were floating freely in the vitreous, also shreds of hyaloid tissue, to which were attached numerous dustlike opacities There was no opacity of any kind to be found in the aqueous or on the back of the cornea and no inflammation was apparent The vision in the right eye was 20/100

Under treatment the vision became better, 20/50, and at one time 20/40 Between June, 1920, and February, 1922, the patient had had four light attacks and one severe one which left the eye almost without a reflex These exacerbations did not come on suddenly as they would have if they had been recurrent hemorrhages From the time of his first visit the patient was urged to have all his pulpless teeth extracted, but several were not removed



Fig 5—Teeth of patient E O M (Case 8) The tooth showing the most marked roentgenographic evidence of infection is indicated by the arrow This tooth showed a severe infection on culture, but the organisms recovered produced no eye lesions in rabbits The lesion produced by the mixed cultures from the four upper incisors is shown in Figure 2 *d*

marked pericorneal injection three days after inoculation. The iritis gradually cleared. The vitreous of the right eye became increasingly hazy. The red reflex was lost entirely, and there was little pupillary light reflex (Fig 2, *c* and Fig 12). The animal died eight days after inoculation. Necropsy was negative except for the eye findings.

The patient's vision at the present time is 15/100.

**CASE 2—Old *nitis*, myopia, detachment of retina.** D S D, a laborer, aged 35 had been losing vision in the left eye since 1902. Vision in the right eye was also markedly impaired. He was able to work but could not read small type. He had suffered from tooth abscesses as long as he could remember.

The left pupil was distorted from adhesions around the iris. There was a secondary cataract of the left eye. The right eye showed a large white area in the fundus with some detachment of the retina. Vision in the right was 12/200, on the left there was only light perception. The patient had a high grade myopia.

The general physical examination was negative. The urine showed no albumin, sugar or pus, and the Wassermann test was negative. Blood examination revealed red cells, 4,160,000; hemoglobin, 80 per cent; white cells, 6,800. The differential count revealed polymorphonuclears, 64.5 per cent,



Fig 4—Radiograph of tooth from which the culture in Figure 1 was made. The lesions shown in Figure 2 *b* and *c* were produced by the intravenous injection of the streptococcus from this tooth.

polymorphonuclear eosinophils, 1 per cent; polymorphonuclear basophils, 1 per cent; small mononuclears, 23.5 per cent; large mononuclears and transitionals, 10 per cent. A roentgenogram revealed ten pulpless teeth, only two of which showed alveolar abscesses. The upper left second molar was extracted on October 5. The patient did not return for the removal of the other pulpless teeth and has not been seen since. The cultures showed a profuse growth in pure culture of *Streptococcus fecalis*. Rabbits 67 and 68 were injected with the broth culture on October 6. No. 67 developed no eye lesions and showed only arthritis at necropsy. Rabbit 68 showed intense lacrymation and pericorneal injection twenty-four hours after inoculation. On October 31, the pericorneal injection was again present. The left eyeball protruded, the cornea was cloudy, and there was some loss of corneal epithelium (Fig 8). The animal was killed. A purulent arthritis and vegetations on the endocardium were found.

**CASE 3—*Indocyclitis*.** H F N, a driver, aged 42, had suffered from attacks of rheumatism for years. Two years ago, his eyes had been red and painful for a few days. Four weeks ago the right eye again became red and painful. Two days later the left eye was similarly affected. Just before the eye trouble began, a tooth had been extracted because it was abscessed.

observed for the past nine months and has had numerous acute attacks of iritis at intervals of two to three weeks. The appearance of the eye in one of the less acute attacks is shown in Figure 2 f.

Following the extraction of the teeth the infection of the right eye flared up.

CASE 5—*Iridocyclitis, uveitis, hyalitis*. G. R., an oil rig builder, aged 31, had had no serious illness except an attack of pneumonia in 1918. Recently he had nycturia. The right eye was struck by a nail in October, 1920. Six weeks later he noticed that he could not see well. In December, 1920, this eye became red and remained so for six weeks. He had had no vision in the right eye since that time. The left eye had also become red a few days before presenting himself.

An examination of the eye on May 22, 1922, showed on the right, evidence of trauma, uveitis and vitreous opacities. Vision was 15/20. The left eye showed a marked hyalitis.

The patient was in an excellent state of nutrition. The tonsils had been removed. The general physical examination was negative. A blood count revealed red cells, 4,080,000, white cells, 12,950, and the following differential count: polymorphonuclear neutrophils, 68.0 per cent, polymorphonuclear eosin-

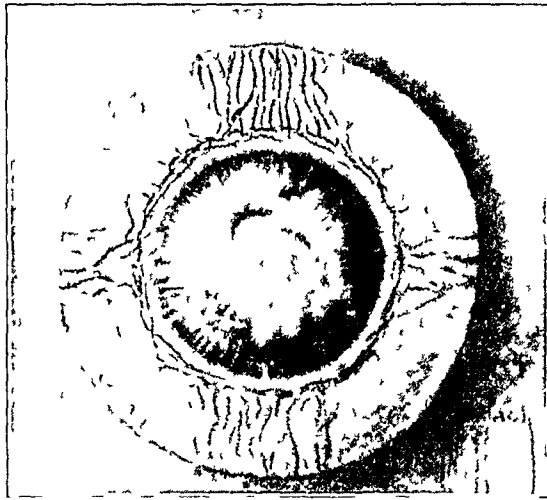


Fig 7—The eye of Rabbit 152 following the intravenous injection of the streptococcus isolated from the pulp and root tip of tooth indicated by arrow in Figure 6.

ophils, 20.4 per cent, polymorphonuclear basophils, 0.4 per cent, small mononuclears, 24.2 per cent, large mononuclears and transitionals, 5.4 per cent. The urine showed albumin and numerous pus cells. The Wassermann test was positive. A dental radiograph showed an alveolar abscess around a root and one pulpless tooth. Cultures showed staphylococci and *St. salivarius*. Four rabbits were injected with the broth cultures. None of the animals showed eye lesions.

CASE 6—*Acute glaucoma*. S. W., a housewife, aged 46, had been having some pain in the right eye for three years. In August, 1922, the pain became much more severe and the eye became red. The condition had been diagnosed and treated as iritis.

When seen on Sept 12, 1922, the pupil of the right eye was dilated. There was a mild pericorneal injection. The intra-ocular pressure was 75 mm (McLean tonometer). Vision was 15/200.

Since the intra-ocular pressure had ceased to respond to eserine, an iridotomy was performed on Jan 17, 1923. When last seen, on March 22, 1923, the intra-ocular pressure was 39 mm. No local treatment had been given since Jan 17, 1923.

Examination of the right eye revealed iris pigment deposits on the anterior capsule of the crystalline lens and posterior synechiae. The iris was slightly muddy in appearance. The left eye was very much congested throughout the eyeball. The cornea was steamy, and there were clusters of keratitis punctata deposits on the back of the cornea. The vessels of the iris were large and could be well seen even through the murky medium of the anterior chamber. The vision in the right eye was 15/15, in the left eye 15/100.

The general physical examination was negative. The tonsils were small. The blood count revealed red cells, 4,312,000, white cells, 8,150, and the following differential count: polymorphonuclear neutrophils, 58.0 per cent, polymorphonuclear eosinophils, 4.4 per cent, polymorphonuclear basophils, 0.6 per cent, small mononuclears, 25.2 per cent, and large mononuclears and transitionals, 11.4 per cent. The urine showed a trace of albumin, a few pus cells and granular casts. The Wassermann test was negative. The roentgenogram revealed only one pulpless tooth, the upper right molar, the mesial root of which showed an alveolar abscess. A pure culture of *Sti salivarius* was obtained from the lingual root, the other roots were sterile.

On August 31, Rabbits 35 and 36 were inoculated intravenously with the broth culture. The following day No. 35 showed marked pericorneal injection and lacrymation. The next morning it was dead. No. 36 showed moderate pericorneal injection seven days after inoculation. On September 2, Rabbit 42 was inoculated with 5 cc of a broth subculture of the original culture. The

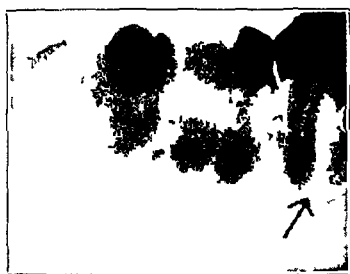


Fig 6—Tooth (indicated by arrow) from Case 12. The eye lesion shown in Figure 7 was produced by the intravenous injection of the streptococcus isolated from the pulp and root tip of the tooth. The first attack of iritis followed the placing of the large filling.

next morning the animal was dead. There was marked pericorneal injection of the right eye. Necropsy was otherwise negative.

**CASE 4—Uveitis following operation for secondary cataract.** M. V., a schoolgirl, aged 16, suffered from congenital cataracts which several years ago had been partly removed by needling, leaving a tough secondary membrane in each eye. One secondary cataract was removed with a good result. Six days after operation on the right eye in October, 1921, the patient had an attack of iridocyclitis, this developed into uveitis, which persisted until June, 1922. The infection became quiet, but the eye remained small and soft, in a condition of phthisis bulbi.

A roentgenogram, Sept. 1, 1922, showed alveolar abscesses around the roots of the upper and lower right first molars and the lower left first molars. Cultures of the upper right molars showed *Sti salivarius* and *Sti nonhemolyticus* I. The other two teeth showed a profuse growth of *Sti nonhemolyticus* I.

Rabbits 43 and 44 were inoculated, Sept. 2, 1922, with the mixed broth cultures. Rabbit 44 developed marked lacrymation and pericorneal injection, which gradually cleared up. Necropsy on September 9 showed a few abscesses in the kidneys and a purulent arthritis. Rabbit 43 showed similar changes in the eye and also some exudate in the anterior chamber. This rabbit has been

An examination of the right eye on May 20, 1922, during a period of active infection showed posterior synechiae, plastic exudates in anterior chamber and a small hemorrhage at the periphery of the iris. There was much pericorneal injection, deep and superficial. The intra-ocular pressure was normal. There was intense photophobia and lacrimation. The left eye showed no active infection, but posterior synechiae were present, indicating that there had been attacks of iritis in this eye also.

A physical examination, on Nov 21, 1922, revealed a well compensated aortic insufficiency. The Wassermann test and urine examination were negative. A blood count revealed red cells, 4,142,000, white cells, 8,350, and the following differential count: polymorphonuclear neutrophils, 68.2 per cent, polymorphonuclear eosinophils, 7.2 per cent, small mononuclears, 17.2 per cent, large mononuclears, 7.4 per cent. A dental roentgenogram revealed nine pulpless teeth, only one of which showed a definite alveolar abscess (Fig 5). The root tip of the lower left first bicuspid showed an infinity of colonies of a green-producing streptococcus in the brain agar cultures. The mixed broth cultures from this tooth and the upper left first bicuspid, however, produced no eye lesions in rabbits. The four upper incisors were removed at one operation. The upper right lateral was sterile even in broth, the left central and lateral showed *St. salivarius* and the central, *St. fecalis*.

Two rabbits (Nos 95 and 96) inoculated with the mixed cultures developed a marked iritis (Fig 2 d). At necropsy one showed cloudy fluid in the joints.



Fig 8—Retouched photograph of the eye of Rabbit 68, twenty-five days after the intravenous injection of organisms from infected teeth in a case of iritis (Case 2)

with an abscess of the kidney. The other had no lesion except that of the eyes. The upper and lower right second molars showed a profuse growth of staphylococci and streptococci. Two rabbits inoculated with the mixed cultures developed marked bilateral circumcorneal injection, with a purulent arthritis and abscesses in the kidney, voluntary muscle, and heart.

**CASE 9—Episcleritis** J W, a housewife, aged 31, had had "blood poisoning" in 1914 following childbirth. The appendix had been removed in 1908, and the tonsils in 1922. Her general health was good. She said that the eye trouble had begun three months previously, with itching of right eye lid and redness of the eye. The symptoms had disappeared under treatment, but had returned one week before. On examination the patient was found to be in an excellent state of nutrition. The heart, lungs and abdomen were negative. There were marked swelling and redness of the right lower lid, with circumcorneal injection and injection of the sclera of the right eye. Blood examination revealed red cells, 4,000,000, white cells, 9,500, and the following differential count: polymorphonuclear neutrophils, 51.6 per cent, polymorphonuclear eosinophils, 2.8 per cent, small mononuclears, 42.8 per cent, and large mononuclears, 2.8 per cent. The urine showed no albumin, sugar, pus or casts. The Wassermann test was not performed. The roentgenogram showed the upper right second bicuspid to be pulpless with no canal filling. The vitality of the adjacent molar



The general physical examination on Sept 22, 1923, was negative. The urine showed a few pus cells. The Wassermann test was negative. The blood count revealed red cells, 4,150,000, white cells, 9,550, and the following differential count: polymorphonuclear neutrophils, 56 per cent; polymorphonuclear eosinophils, 26 per cent; polymorphonuclear basophils, 14 per cent; small mononuclears, 35.2 per cent; large mononuclears and transitionals, 48 per cent. A roentgenogram showed one alveolar abscess and two other pulpless teeth without apparent infection. Cultures of the extracted teeth showed *Staphylococcus aureus* and streptococci.

On September 14, Rabbits 57 and 58 were inoculated with the mixed cultures. On September 15, Rabbit 57 showed bilateral circumcorneal injection with exudate on the iris. The animal was killed. No other lesions were found. Rabbit 46 developed moderate pericorneal injection, which gradually disappeared. At necropsy, only a purulent arthritis was found.

CASE 7—*Glaucoma, recurrent iritis, high myopia*. E. B., a housewife, aged 46, had had several hemorrhages from the stomach in 1902. She complained of nycturia and frequent micturition during the day. She began to have pain in left eye four years before. An operation was performed on the left eye for glaucoma one year later. She gradually lost vision in the right eye. An operation for glaucoma was performed on the right eye, June, 1922. She had had an acute attack of iritis in the left eye for a week before presenting herself.

The right eye showed past iritis by the presence of an organized pupillary membrane which was not attached to the lens and which, when the pupil was contracted, would stretch out and impede the light. This was of long standing. Intra-ocular pressure was reduced to normal by iridotomy operation. In September, 1922, during the attack of iritis, there were some dots of keratitis punctata and pericorneal injection in the left eye.

The general physical examination was negative. Her tonsils were small, without apparent infection. Blood examination revealed red cells, 4,020,000; white cells, 10,500, and a differential count: polymorphonuclear neutrophils, 73.4 per cent; polymorphonuclear eosinophils, 26 per cent; small mononuclears, 17.8 per cent; large mononuclears, 6.2 per cent. Urine examination and the Wassermann test were negative. A roentgenogram showed nine pulpless teeth, two of which showed definite alveolar abscesses. The teeth were extracted in four groups.

One of two rabbits injected on Sept 15, 1922, with the mixed cultures from the upper right and left central incisors developed iritis. No eye lesions were produced by the mixed cultures from the upper right second bicuspid and the first and second molars. Two rabbits (Nos 69 and 70) developed iritis after the intravenous injection of the mixed cultures from the lower right second bicuspid and first molar. Rabbit 70 also developed meningitis. Cultures from the anterior chamber of the eye showed many colonies of streptococci and a few colonies of staphylococci. Rabbits 71 and 72 were injected with the cultures recovered from the eye of Rabbit 70. Both developed iritis and died the following day. Rabbits 74 and 75 injected with the cultures from the left lower first bicuspid and the second molar, also developed iritis. One died the following day, the other was kept for three weeks, when it showed marked bulging of both eyes with pericorneal injection. Rabbits 85 and 86 injected with a culture from the root tip of a tooth with a dying pulp developed acute iritis and meningitis.

CASE 8—*Recurrent iritis*. E. O. M., a clerk, aged 32, had had the first attack of iritis in 1905 and the second in 1909. Following this he had had frequent attacks at intervals of about one year. During the past two years he had suffered from iritis almost continuously in a subacute form. The patient said that the most severe attack he had ever had occurred while some dental work was being done. He had been confined to bed for four months in 1920 with rheumatism.

Two rabbits injected from three of the extracted teeth developed no eye lesions. The lower left central and lateral incisors showed *St. fecalis* in pure culture. Rabbits 134 and 139 were inoculated with these mixed cultures. Rabbit 134 developed an iritis of one eye which gradually cleared up. Necropsy revealed only a purulent arthritis. Rabbit 139 developed a marked bilateral pericorneal injection, which continued until the animal was killed ten days later. The only necropsy finding was cloudy fluid in the joints.

The patient had a complete recovery with vision 13/15. He was given subcutaneous injections of milk also, so it is difficult to determine just what effect the extraction of the teeth had.

CASE 12—*Uveitis*. Mrs. F. T., a housewife, aged 43, had had typhoid fever in 1914 and rheumatism during the past year. Her eye trouble began in 1912, with a severe attack of iritis with almost complete loss of vision in the left eye.



Fig. 9—Portion of iris and ciliary body of eye of Rabbit 95 (Fig. 2 d)

A second attack occurred in 1916. She had no further trouble until December, 1922, when iritis again occurred in the left eye, followed by another attack in January, 1923. When first seen on March 1, 1923, there was no light perception, and the eye showed that the whole uveal tract had been involved. The patient said that a large filling had been placed in the right lower first molar in 1912. The tooth became very painful. The filling was removed to "let the gas out" and replaced. The first attack of iritis developed soon after the tooth trouble. An examination of the right eye showed no light perception, posterior synechiae, without active infection. The vision in the left eye was 20/20. There were posterior synechiae, but no inflammation.

The patient was undernourished. The tonsils were small. The general physical examination was otherwise negative. Blood count revealed red cells, 4,300,000, white cells, 8,700, and the following differential count: polymorphonuclear neutrophils, 66.4 per cent, polymorphonuclear eosinophils, 2.6 per cent, polymorphonuclear basophils, 0.8 per cent, small mononu-

was questionable. These two teeth were extracted. The bicuspid showed a profuse growth of staphylococci and *Str fecalis*. The molar also showed streptococci and staphylococci.

Rabbits 87 and 88 inoculated with the mixed cultures died forty-eight hours later. Rabbit 87 showed a marked hemorrhagic iritis with fluid in the anterior chamber (Fig 2 c) and multiple small abscesses in the kidneys. Rabbit 88 showed a few hemorrhages in the iris and sclera and kidney abscesses.

CASE 10—*Monocular acute conjunctivitis with corneal abscesses, iritis*. J. P., a clerk, aged 60, had been blind for three years. There had been no pain or inflammation, but vision had been very dim and gradually became worse eight years previous to this time.

Examination on Nov 10, 1921, showed a fully developed cataract in the right eye, with good light projection. There was a partly absorbed cataract, with calcification in the left eye. This was removed, and the eye went on to perfect healing with a vision of 15/30. The right eye was operated on without complication except that it remained red longer than the usual time. In six weeks it had become quiet. Vision after injection was 10/30. On Nov 22, 1923, the right eye was very painful and red, with much pus in the conjunctival sac. There were numerous small grayish ulcers in the cornea, superficial and gray striations in the posterior layers, with a slightly congested iris. There were also small grayish abscesses in the corneal tissue. For days later there was exudate in the anterior chamber. The conjunctivitis probably followed the breaking of a small corneal abscess and might have come from within.

The general examination, on Nov 25, 1922, was negative. The blood count revealed red cells, 4,140,000, white cells, 10,200, and the following differential count: polymorphonuclear neutrophils, 65.0 per cent; polymorphonuclear eosinophils, 2.4 per cent; polymorphonuclear basophils, 0.8 per cent; small mononuclears, 23.4 per cent; large mononuclears, 8.4 per cent. The urine showed a trace of albumin and sugar. The Wassermann test was negative. The dental roentgenogram showed one broken tooth with bone destruction around the root end. Seven other teeth showed extensive pyorrhea.

Two rabbits were inoculated on Nov 26, 1922, with the mixed culture from four of the extracted teeth. On November 27, Rabbit 104 had developed a marked pericorneal injection of the right eye, which persisted until the animal was killed four days later. Necropsy revealed endocardial vegetations, kidney abscesses and purulent arthritis. Rabbit 105 developed a slight injection of the right eye, with similar necropsy findings. Rabbits 101 and 102 were inoculated with the mixed cultures from the remaining extracted teeth. Rabbit 101 developed a hemorrhagic iritis, and the other a marked circumcorneal injection of one eye. Both animals showed abscesses of the kidneys and a purulent arthritis at necropsy.

CASE 11—*Ulceration of cornea*. S. K., a farmer, aged 62, had suffered from rheumatism at intervals for thirty years. He had also had "lumbago" at times. His present trouble began on Aug 1, 1922, with pain and redness of the right eye, which his physician thought was due to an iritis. At the same time he had an eruption on the right side of the face and body. The eye improved under treatment, but the symptoms returned later and have persisted. Examination of the right eye showed an ulcer in the superficial layers of the cornea in the center of the pupil. There is no sign of iritis at present. There was much pus in the meibomian glands and thickening of the lids. Vision was 15/200. The tonsils were small. The general physical examination was negative. Blood count revealed red cells, 4,144,000, white cells, 9,550, and the following differential count: polymorphonuclear neutrophils, 72.2 per cent; polymorphonuclear eosinophils, 3.8 per cent; polymorphonuclear basophils, 1.2 per cent; small mononuclears, 19.2 per cent; and large mononuclears, 3.6 per cent. The urine contained no albumin or sugar. The Wassermann test was anticomplementary. The dental roentgenogram showed multiple pulpless and infected teeth.

5,824,000 red cells, 7,900 white cells, hemoglobin 116 per cent, and the following differential count polymorphonuclear neutrophils, 63.2 per cent, polymorphonuclear eosinophils, 2 per cent, polymorphonuclear basophils, 0.2 per cent, small mononuclears, 31.0 per cent, and large mononuclears, 5.6 per cent. The roentgenogram showed only one pulpless tooth which had a large cavity and an alveolar abscess. A culture of the root tip showed a staphylococcus and *St. salivarius*. The organisms grew only near the bottom of the culture tube.

Rabbits 176 and 177 were inoculated with the cultures of root tips and curettings on March 3, 1923. Rabbit 176 showed pericorneal injection, which gradually increased in intensity. At necropsy on April 10, only a purulent arthritis was found. Rabbit 177 developed no eye lesions and showed only a healing arthritis at necropsy. Rabbits 178 and 179 were injected on March 3, with the cultures from the curettings of the tooth socket only. Three hours after



Fig. 11—Eye showing marked infiltration of choroid

inoculation both animals showed an extreme pericorneal injection. Rabbit 178 continued to have a moderate pericorneal injection, and as late as May 3 had an acute attack of iritis. Rabbit 179 was killed twenty-five days after inoculation and showed only a healing arthritis.

CASE 14—*Acute iritis with arthritis*. E. E., a housewife, aged 38, said that her present trouble had begun two weeks previously with pain in most of the large joints. There was no swelling or redness. One week before she noticed an eruption on the forearms and back of the neck, beginning as red macules which gradually spread as they cleared in the center. For several days her eyes had been red. The patient was much undernourished. The skin eruption appeared to be an erythema multiforme. Her tonsils were small. The submental glands were large and painful on pressure. There was some excess fluid in the right knee. The larger joints were painful on motion. The left eye presented the picture of a mild iritis. The blood count showed red cells, 3,056,000, white cells, 10,750, and the following differential count polymorpho-

clears, 28.2 per cent, and large mononuclears, 20 per cent. All the upper teeth had been extracted. A roentgenogram showed no apparent bone infection in the upper jaw. There were no pulpless teeth in the lower jaw. The right lower first molar had a large silver filling, was tipped forward, and had a pocket around it (Fig 6). The tooth responded, however, to tests for vitality. This tooth was extracted. On opening the pulp chamber under sterile precautions it was found that the pulp chamber had been encroached on by secondary dentine formation. The nerve was injected and edematous and showed a pure culture of *St. mitis*. The same organism was obtained in the culture of the root tips. Rabbits 152 and 153 were inoculated with the mixed cultures from the pulp and root tip on Feb 2, 1923. Rabbit 152 developed an extreme pericorneal injection which was less marked the following day. On February 7, the circumcorneal injection had returned in the right eye. There

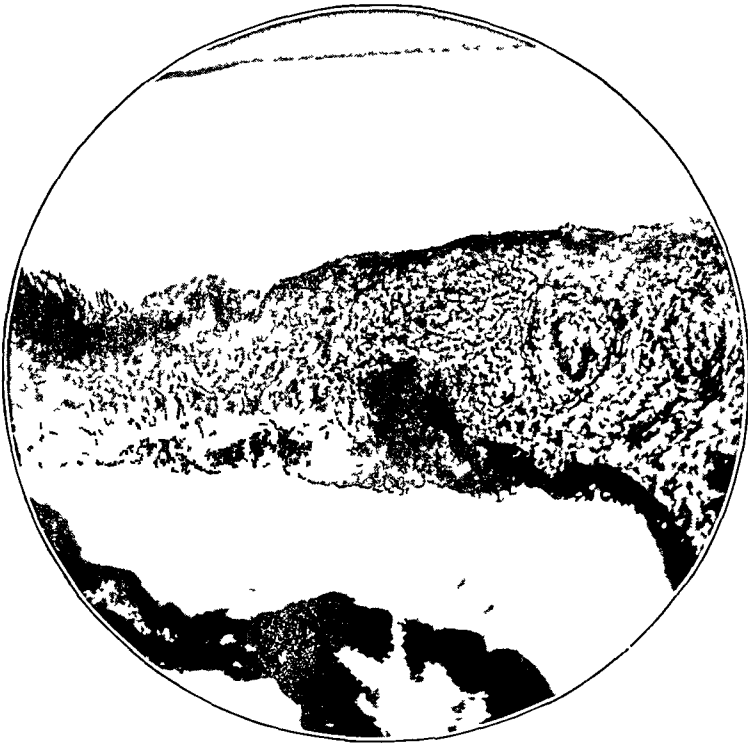


Fig 10 —Iris showing area of small round cell infiltration

were multiple hemorrhages in the iris and cloudy fluid in the anterior chamber (Fig 7). Necropsy revealed also abscesses of the kidneys, white streaks in the muscles and a purulent arthritis. Rabbit 153 showed only cloudy fluid in the joints.

CASE 13—*Iridocyclitis, uveitis, hyalitis*. J. R., a salesman, aged 22 had a "nervous breakdown" in October 1922. He had never been ill before. In December, 1922, he noticed that the vision in the right eye was blurred. The condition improved, but the dimness of vision recurred and had grown steadily worse. The patient could recognize hand movements at 0.5 meter. The eye was a little softer than usual. The back of the cornea was almost covered with small round dots of exudate (keratitis punctata). The eyeball was moderately red and the pupil round, but there were some posterior synechiae. The vitreous was one mass of floating opacities. The patient was well nourished. The tonsils were large, but no free pus could be expressed. The general physical examination was otherwise negative. The blood count showed

suffered from stiffness in the right knee and frequent attacks of redness of the right eye, lasting from one to three days. The patient was in an excellent state of nutrition. There was moderate pericorneal redness of the right eye. The tonsils were small. The blood count showed 7,700 white corpuscles, and the following differential count: polymorphonuclear neutrophils, 73.0 per cent, polymorphonuclear eosinophils, 1.0 per cent, polymorphonuclear basophils, 0.4 per cent, small mononuclears, 20.6 per cent, large mononuclears, 5.0 per cent. There was a trace of albumin and numerous pus cells in the urine. The Wassermann test was negative. A roentgenogram showed marked pyorrhea around the lower first molar with interradiol bone absorption. The tooth contained a large filling. *St. mitis* was recovered from the root tips and a green-producing streptococcus from the pulp in pure culture. Rabbits 164 and 173 were inoculated with the streptococcus recovered from the pulp. Both animals developed a pericorneal injection and at necropsy showed many white streaks in the muscles and a purulent arthritis. The two animals inoculated with the cultures from the root tip developed no eye lesions. Many abscesses in muscles and kidneys were found at necropsy.

The patient's joint and eye symptoms disappeared quickly after the extraction and have not recurred.

nuclear neutrophils, 70.4 per cent, polymorphonuclear eosinophils, 1.4 per cent, polymorphonuclear basophils, 0.8 per cent, small mononuclears, 19.4 per cent, and large mononuclears 8.0 per cent. The urine contained a trace of albumin but no sugar, pus or casts. The Wassermann test was negative. A roentgenogram revealed fifteen pulpless teeth, several of which showed alveolar abscesses. Rabbits 190 and 193 were inoculated on March 28, 1923, with the mixed cultures from six extracted teeth. Both developed extreme pericorneal injection within a few hours. Rabbit 190 was killed on April 4, and showed purulent fluid in the joints, endocardial vegetation and a few kidney abscesses. The pericorneal injection in Rabbit 193 had disappeared the day following the



Fig 12—Vitreous of eye shown in Figure 2 c. Note the infiltration of cells in the vitreous humor.

inoculation. It was again present on March 3, when the animal was killed. A pure culture of a green-producing streptococcus was recovered from the iris. A meningitis and purulent arthritis were also present. Four other animals were inoculated with cultures from other teeth. Two developed iritis, and all showed a purulent arthritis at necropsy.

Following the extraction of the first teeth the patient had an exacerbation of the arthritis. The iritis and skin eruptions disappeared within a few days. The arthritis had cleared entirely within four weeks.

CASE 15—*Recurrent uveitis with arthritis*. L. S. L., a housewife, aged 47, had always enjoyed excellent health until recently. During the past year she had

individual cages. These cages were located in an unheated shed which protected the animals from wind and rain but which afforded them ample sunshine and ventilation. The date of birth of many of the rabbits was known and we were thus able to determine whether age played a part in the causation of the lesions.

The first group, consisting of eight animals to which the diet containing meat was fed, were brought to the laboratory when half grown. For the next two months they were fed the stock laboratory diets. At the end of this period they appeared to be in excellent condition and in no case did the urine contain albumin. They then began to eat the experimental diet containing one part of the dried beef to two parts of the flour. On June 4, 1919, one week after the beginning of the experiment, the urines of five of the rabbits were examined. Three were alkaline, two neutral, and all gave definite reactions for albumin. The sediments contained no abnormalities. On June 17, a few hyaline and granular casts were found in some of the specimens examined. By July 9, six weeks after the beginning of the experiment, both albumin and casts were found in the urine of every rabbit in the group.

Evidence was thus obtained which indicated that the ingestion of a meat containing diet by rabbits will result, within a few weeks, in an abnormal state of the kidneys.

One of the eight rabbits lived five months, and two of them lived seven months on the diet.

The first of these rabbits was found on Oct. 15, 1919, lying on its side and was unable to maintain the standing position. No twitching was observed, and the breathing was normal. It weighed 2,090 gm. It was killed by a blow on the head, and necropsy immediately performed. The bladder urine was slightly acid to litmus, had a specific gravity of 1.020, contained 0.7 per cent albumin (Esbach), and the sediment showed many granular and hyaline casts but no leukocytes or red blood corpuscles. The kidneys weighed 25.5 gm,<sup>3</sup> the surface was smooth and dark red. The cut surface was dark, congested and "glassy," with a few white streaks in the cortex. The aorta showed extensive atherosclerosis. The liver was firmer than normal and on section gave the appearance of cirrhosis. The remainder of the organs were grossly normal. Nothing suggesting infection as a cause of death was seen.

The second of these three rabbits developed an increasing indifference to his surroundings during the few days preceding his death, accompanied by a gradual loss of appetite. On Jan. 6, 1920, he refused food entirely. He weighed 2,310 gm. He was killed by bleeding. The bladder urine showed a well marked albuminuria and numerous granular and hyaline casts but no leukocytes or red blood

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3 The kidneys of normal adult rabbits weigh from 5 to 6 gm per kilogram



# RENAL INJURY PRODUCED IN RABBITS BY DIETS CONTAINING MEAT<sup>1</sup>

L H NEWBURGH, MD

AND

SARAH CLARKSON, MS

ANN ARBOR, MICH

In a recent communication<sup>1</sup> we described the atherosclerosis which is produced in rabbits that are fed diets rich in meat proteins. The kidneys of the same rabbits presented abnormalities which form the subject of this paper.

The composition of the diets and the selection and care of the animals was described in the previous paper in the following words:

The animals were fed diets containing two different concentrations of protein. Lean beef muscle mechanically freed of fat and then dried and powdered<sup>2</sup> was the chief source of protein. Ordinary white bread flour mixed in equal parts with bran, supplied carbohydrate and roughage. The first diet was made by stirring together 1,000 gm of the powdered beef, 2,000 gm of the flour, bran mixtures, 20 gm sodium chlorid, 50 gm baking powder and enough water to produce a stiff dough. The latter was then spread thickly in oiled pans and baked in an oven at about 180 C until a dark brown crust had formed.

The second diet contained 500 grams of powdered beef, 2,000 gm of the flour-bran mixture, 20 gm of sodium chlorid and 50 grams of baking powder. It was prepared for feeding in the same way as the first diet.

An analysis for nitrogen, by the Kjeldahl method, of the powdered beef and of the two diets, gave the following values:

100 gm dried powdered beef	= 13.0 gm N
100 gm first diet	= 5.8 gm N
100 gm second diet	= 4.3 gm N

Multiplying these nitrogen figures by 6.25 gives the following protein content:

Dried powdered beef	= 81.2% Protein
First diet	= 36.2% Protein
Second diet	= 26.8% Protein

In addition to this food, the rabbits were each allowed about 100 gm of greens once a week.

The animals were obtained from fanciers who had taken special pains to raise them in clean, light, well ventilated pens. During the feeding experiments they lived in pens which had previously been made scrupulously clean and which were kept clean thereafter. Some of the rabbits were housed together in small groups. Many others lived throughout the experiment in

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\* From the Department of Internal Medicine, University of Michigan Medical School.

1 Newburgh and Clarkson. The Production of Atherosclerosis in Rabbits by Feeding Diets Rich in Meat. Arch Int Med **31** 653 (May) 1923.

2 This material was obtained from the Digestive Ferments Co., Detroit.

This feeding experiment, performed in 1919 with a diet containing 36 per cent of protein, was repeated in 1922. The results obtained in the earlier series were confirmed by the data from the later group of rabbits. Figures 2, 3, and 4 are photomicrographs of the kidney of one of these rabbits (No 140) of the 1922 group that lived on the diet for twenty-seven weeks.

NEPHROPATHY OF RABBITS WHOSE DIET CONTAINED 27 PER  
CENT OF PROTEIN

The nephropathy described above occurred in rabbits that had been eating a diet with a protein content of about 36 per cent. It was

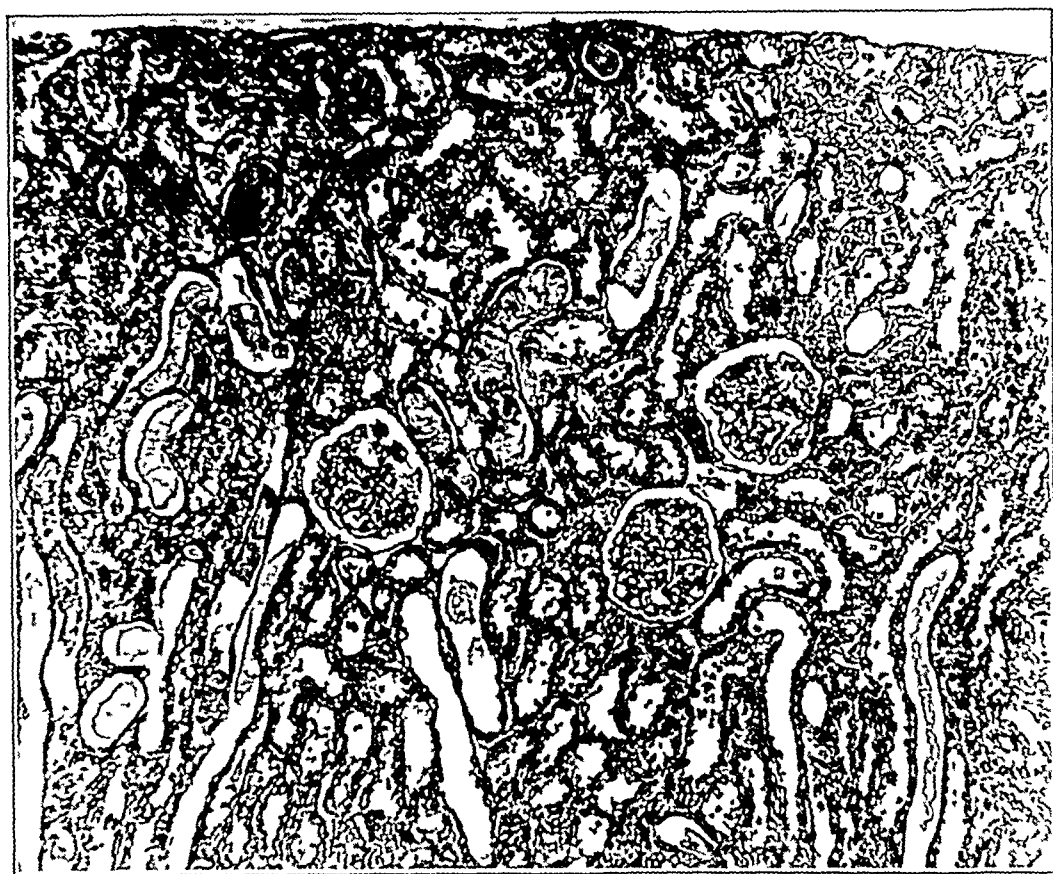


Fig 2—Subcapsular portion of cortex of a rabbit that had eaten a diet containing 36 per cent of protein for about six months. Dilatation of tubules and flattening of their lining membrane is well marked but not so extreme as that shown in Figure 1. The glomeruli are normal and fibrosis is absent. Casts are numerous.

accordingly of interest to study the kidneys of rabbits whose food contained less protein. A large number of animals whose diet contained 27 per cent of protein were available for this purpose. These animals may be divided into two lots—Group A containing the rabbits that lived on the diet less than twenty-four weeks and whose kidneys in no case showed chronic lesions attributable to the diet, and Group B, consisting of animals that took the diet from twenty-four

cells. The kidneys weighed 22 gm, but presented no definite abnormalities to the unaided eye. The aorta showed extensive atherosclerosis. The remainder of the organs appeared to be normal, and no evidence of infection was seen.

The third rabbit, on Dec 24, 1919, was limp, trembling, dyspneic and unable to maintain the erect position. He weighed 2,380 gm. He was killed by a blow on the head. The bladder urine was dark, contained a large amount of albumin, many hyaline, granular and cellular casts, but no leukocytes or red blood cells. The kidneys weighed 32.5 gm, and were dark brownish red. The capsule stripped

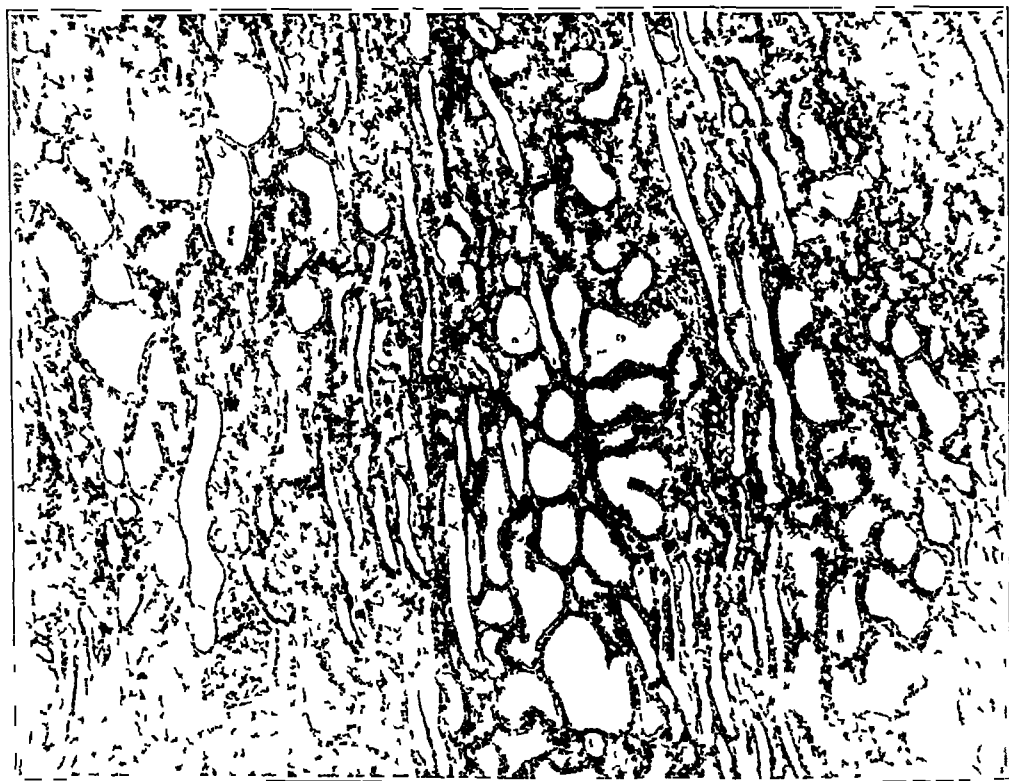


Fig 1—Midcortical portion of the kidney of a rabbit that had eaten a diet containing 36 per cent of protein for seven months. The tubules are greatly dilated and their lining epithelium is much flattened. The glomerulus is apparently normal. No fibrosis is to be seen. Casts are numerous.

easily, leaving a smooth surface. On section, the organ dripped blood. The cortex protruded above the general surface, was "glassy" and presented many minute hemorrhagic points and streaks. The aorta showed extensive atherosclerosis. The liver was firmer than normal and on section presented the markings suggestive of cirrhosis. The other organs were normal, and no evidence of infection was noted. These gross evidences of disease of the kidneys were confirmed by microscopic examination. Figure 1 is a photomicrograph of a section from the kidney of the third rabbit.

*Group B*—This group contained twelve animals. The kidneys of nine of them showed extensive chronic lesions, most marked in the cortical portion of the tubules. The microscopic picture presented by these kidneys closely resembled that already described (Figs 1, 2, 3 and 4) for the animals that had lived from five to seven months on a diet containing 36 per cent of protein.

In both groups the nephropathy was notable for its diffuse character. The dilatation and atrophy of the tubules frequently extended with varying degrees of intensity across the whole section, or, in a

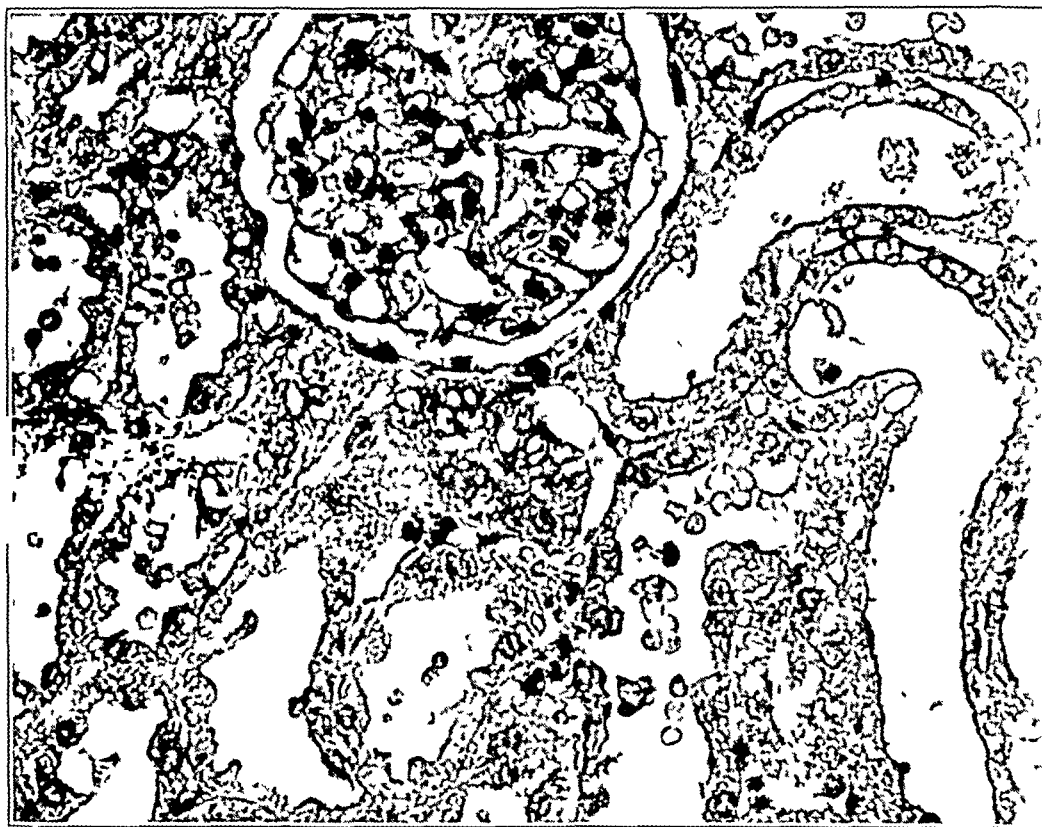


Fig 4—Still higher magnification of a portion of the field seen in Figure 2, showing the presence of red blood corpuscles in the lumina of the tubules, and the flattening, granulation, vacuolization and desquamation of the tubular epithelium.

few instances, was broken up into broad irregular patches separated by a few tubules whose cells were only slightly or not at all atrophied. Nowhere were the cells of the tubules normal. The glomeruli showed no injury or minor degrees of injury and were not scarred. The dilated tubules were not embedded in fibrous tissue, nor was there any general increase in fibrous tissue. The disease, from the histologic point of view, appeared to be restricted to the lining cells of the tubules. In rabbits that had eaten the diet only a few weeks, these cells showed the well-known picture of acute and subacute degeneration. The renal

to fifty-nine weeks, in 75 per cent of which chronic renal lesions were seen

*Group A*—There were thirty-three animals in this group. Nine of them died of pneumonia early in the experiment. In the remainder the only gross abnormality regularly revealed by necropsy was the presence of kidneys which were considerably larger than normal. In every instance in which bladder urine was obtained at necropsy there existed a marked albuminuria, and many casts were found in the

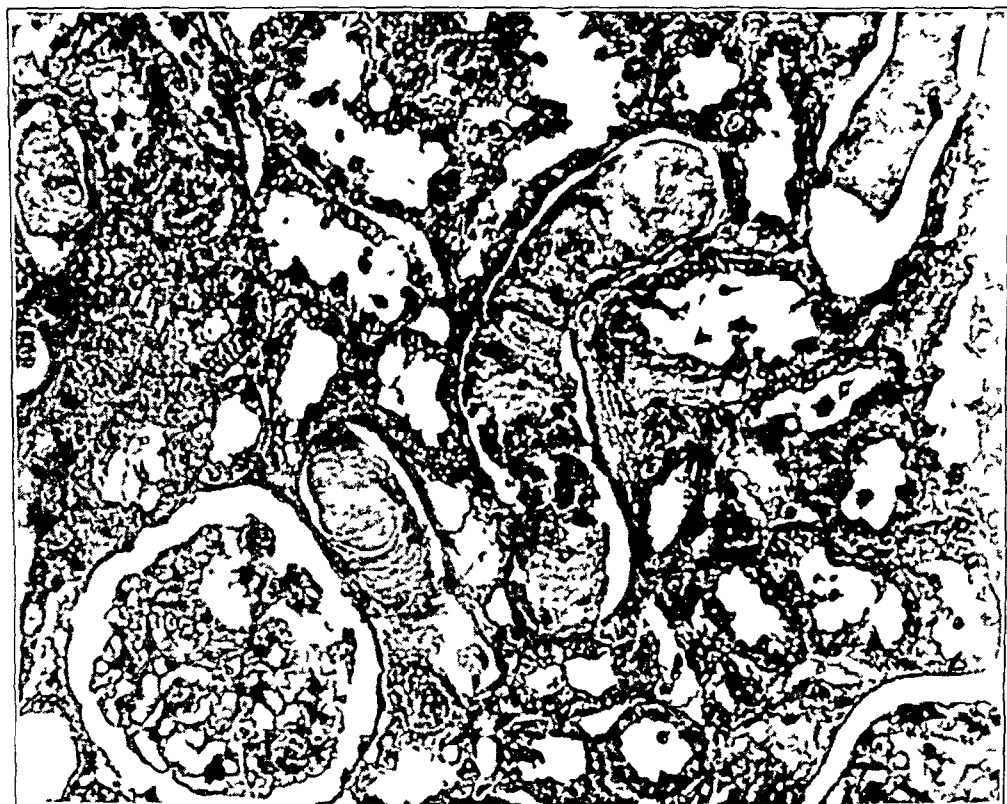


Fig 3—Higher magnification of a portion of the field seen in Figure 2 to show in particular the character of the casts

sediment. The microscopic examination of the kidneys of the animals in which no pneumonia was found regularly disclosed varying degrees of acute parenchymatous injury. The cells of the convoluted tubules appeared to have suffered most. In some cases the lumina of the tubules were closed by the swelling of the cells. Extensive desquamation, vacuolization and granular degeneration were seen in the convoluted tubules of most of the kidneys. Casts were always a prominent feature, and sometimes they were numerous. Minor changes in the glomeruli were sometimes noted, but no true acute glomerulitis was seen.

is indented by bluish stellate scars and deep pits or grooves. The number of these depressions is highly variable. Under the microscope these pits are seen to be the outer surface of a band of contraction, consisting of a strip of fibrous tissue in which are found one or several more or less completely scarred glomeruli and several atrophied tubules. These lesions are always definitely focal in character, occurring as sharply circumscribed bands extending from the capsule, through the cortex deep into the medulla. The glomeruli and tubules beyond the band are usually normal, and both atrophy and scarring are restricted to the band.

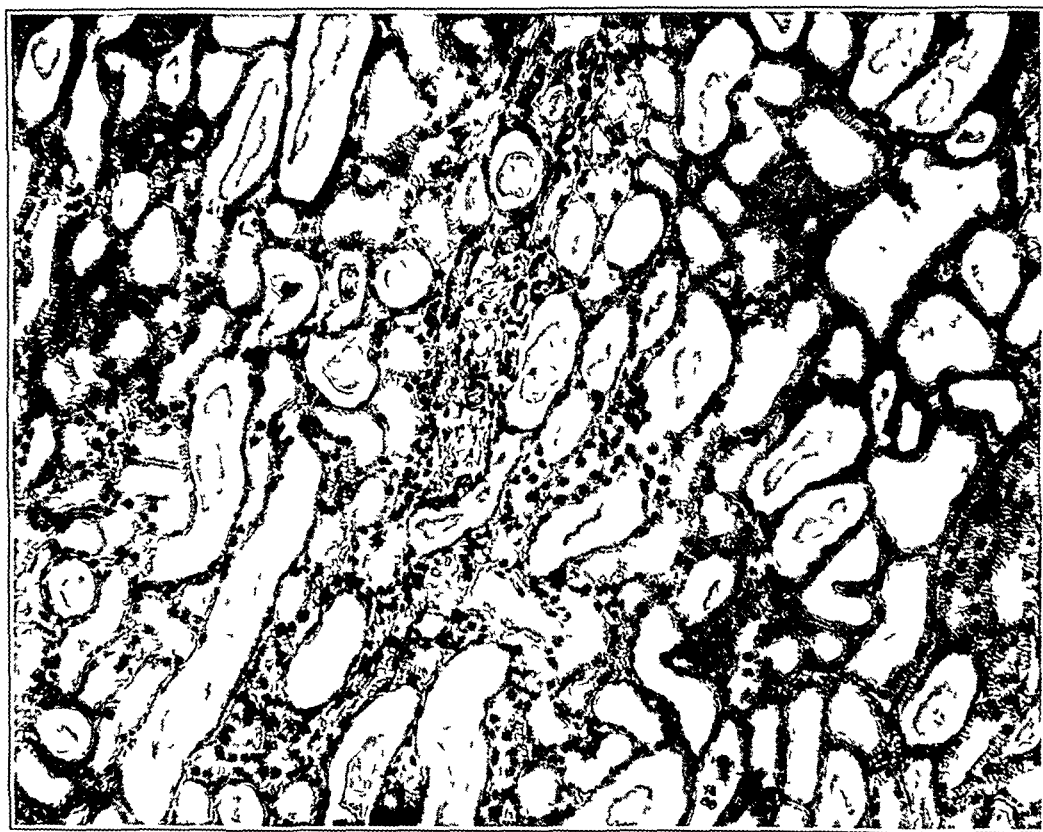


Fig 6—Lower cortical portion of the kidney of a rabbit that had eaten a diet containing 27 per cent of protein for eight months. Here again the widespread dilatation of tubules is the characteristic abnormality.

#### KIDNEY LESIONS IN RABBITS LIVING ON A STOCK DIET

In order to control our work properly, it was necessary to determine how often such lesions were found in rabbits that lived in the laboratory for many months on a stock diet, and whether such lesions in control rabbits ever were widespread and diffuse, that is, whether the diffuse tubular disease seen in the kidneys of the Group B rabbits could have been caused by conditions resulting from prolonged residence in the laboratory in the absence of the meat diets.

tubules of rabbits that had lived on the diet for months showed much desquamation and a lining membrane whose cells had undergone varying degrees of flattening, finally being changed into pavement epithelium. In some tubules the lining membrane had entirely disappeared.

This progressive atrophy of the renal tubules was unattended by any significant changes in the glomeruli or blood vessels or interstitial tissue that could be recognized by means of the microscope.

Figures 5 and 6 are photomicrographs of the kidneys of two of these rabbits (Nos. 67 and 118) that had been on the diet six and one half and eight months, respectively.

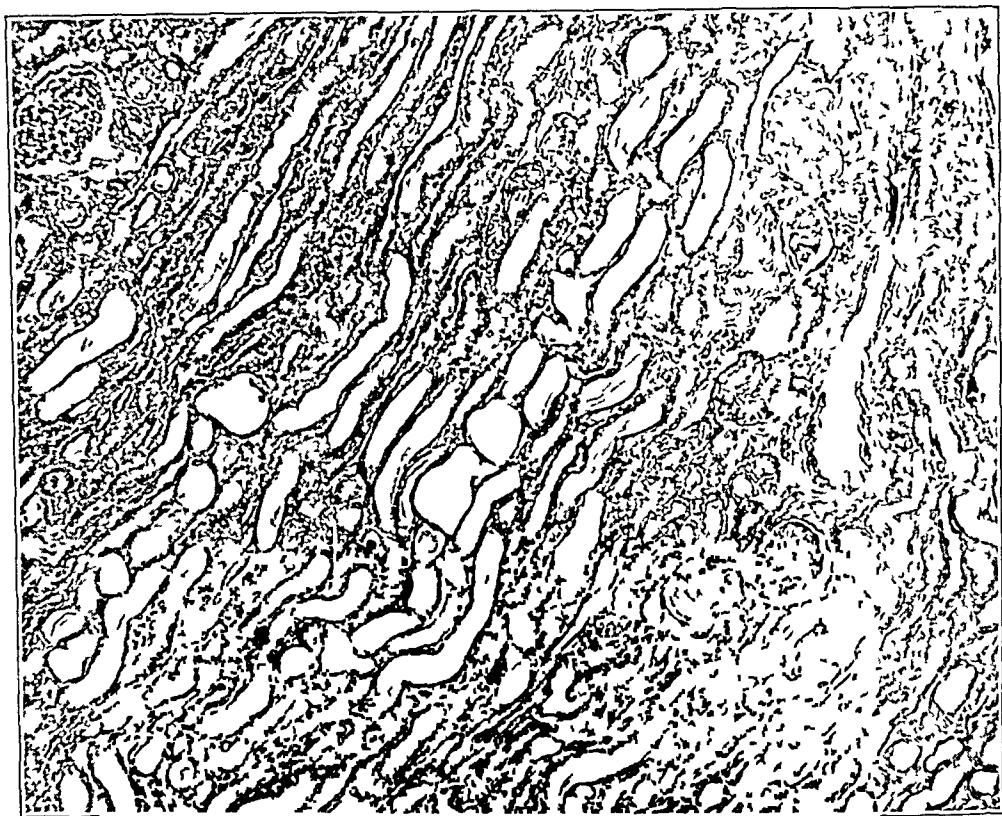


Fig 5—Cortical portion of the kidney of a rabbit that had eaten a diet containing 27 per cent of protein for six and one half months. In general, the changes closely resemble those seen in Figure 1. There is the same widespread dilatation of tubules without fibrosis or scarring of glomeruli.

The kidneys of three of the rabbits in Group B that had been on the diet as long as any of the group did not show these chronic tubular changes. This brings up the question whether the tubular dilatation and atrophy found in 75 per cent of the kidneys was caused by the diet. It is well known to laboratory workers that the kidneys of untreated rabbits are frequently abnormal. If one inspects carefully the kidneys of laboratory rabbits, one will find many whose surface

absence of such lesions in other parts of the field. There is a striking difference between the pathologic process in this kidney and that found in the meat eating rabbits (Figs 1 to 7).

The contrast between the diffuse character of the tubular dilatation, the absence of glomerulitis and the absence of scar tissue in the kidneys of the meat fed animals, when compared with the focal tubular dilatation, the presence of scarred glomeruli and of bands of fibrous tissue seen in the controls, is so great as to make it certain that the



Fig 7—Higher magnification of a portion of the field seen in Figure 5 to show the changes in the lining membrane of the tubules. Some of the tubules which show the greatest dilatation appear to have lost their parenchymatous cells.

nephropathy found in the kidneys of at least the majority of the meat eating rabbits was a product of the diet.

Table 2 contains brief notes about all the rabbits that lived on the meat containing diets for twenty-four or more weeks—sixteen rabbits in all. The renal tubules of twelve of them showed atrophy. In nine (B3, A4, 140, 61, 67, 88, 77, 78 and 118) of these twelve rabbits, the histologic picture presented by the kidney was such that it could not easily be confused with the scarring and atrophy occasionally



For this purpose nineteen rabbits were set aside in a stock cage and given the ordinary laboratory care and food. No attempt was made to protect these animals from infection, on the contrary, we tried to emphasize the effect of the usual laboratory infections on the kidneys by leaving infected rabbits in the pen instead of removing them and isolating them according to our usual procedure. Several of the animals died of pneumonia within the first few weeks. Many of the others acquired "snuffles" early in the experiment. Three of the animals had received intravenous injections of bacteria for the purpose

TABLE 1—*Data From Thirteen Control Rabbits that Lived Six Months or More*

No	Duration, Weeks	Weight at Necropsy, Gm	Kidney			Notes
			Weight, Gm	Gross Appearance	Microscopic Examination	
1	25	1,670	8			
5	26	1,200	11	No scars	No abnormalities	Severe diarrhea
12	45	1,010	13	Very few small scars	No abnormalities	Purulent bronchopneumonia, empyema
37	50	1,450	13	Many scars	Scattered small areas of round cell infiltration	
52	57	2,650	13	No scars	No abnormalities	Bronchopneumonia, petechial hemorrhages of liver, minge
68 X	40	870	10	No scars	No abnormalities	Prolonged snuffles, great emaciation
71	64	3,000	13	Many deep scars	One band of atrophy and fibrosis, cysts in this band otherwise no abnormalities	Severe minge
74	26	940	9	Very few scars	No abnormalities	Emaciation
81	30	1,690	15	No scars	No abnormalities	
83	51	1,380	13	Many scars	Few cysts, otherwise normal	Six intravenous injections of <i>Streptococcus hemolyticus</i> , minge emaciation
84	40	1,110	11	No scars	No abnormalities	Six intravenous injections of diphtheria bacilli, minge emaciation
86	22	1,370	13	No scars	Few small areas of moderate dilatation of tubules	Six intravenous injections of killed typhoid bacilli, six intravenous injections <i>Streptococcus hemolyticus</i> , caseous pneumonia, synechia cordis
A X	58	1,727	10			

of producing immune serums several months before they were set aside as controls. The group as a whole was undernourished and listless. Skin diseases became prevalent, and in some cases resulted in suppuration. All but one of the animals eventually died of infection. Thirteen of the rabbits lived six months or longer, but unfortunately the kidneys of two of them were lost through a technical error.

Table 1 presents the significant data in regard to these thirteen animals. It will be seen that scarring of the surface of the kidney was fairly common, but the microscope showed dilatation of tubules in only one case. The photomicrograph of this kidney (Fig. 8) demonstrates the sharply focal character of this lesion and the entire

TABLE 2—Data From Sixteen Rabbits Fed a Meat-Containing Diet  
for More Than Six Months

Four Rabbits Whose Diet Contained 36 per Cent Protein					
No	Duration, Weeks	Weight at Necropsy Gm	Kidney		Microscopic Examination
			Weight, Gm	Gross Appearance	
B 3	30	2,870	22	Coarsely granular surface no deep pits	Great atrophy and dilatation of tubules, widespread and not related to the small patches of fibrosis, many casts
A 4	30	2,380	32	Surface smooth, no scars	Great atrophy and dilatation of tubules uniformly distributed, few small areas of fibrosis, many casts
138*	34	3,320	20	Few old scars	Many areas of round cell infiltration, no chronic changes
140	27	2,550	28	Occasional small scars	Diffuse tubular atrophy throughout cor- tex, intense parenchymatous injury, many casts
Twelve Rabbits Whose Diet Contained 27 per Cent Protein					
26	44	2,170	22	Some stellate scars	Irregular areas of round cell infiltration, bands and patches of contraction and atrophy, no broad areas of tubular atrophy
27	41	1,930	23	Many irregular de- pressed scars, a number of narrow yellow streaks extend from capsule to medulla	Several bands, each consisting of scarred glomeruli and dilated tubules embed- ded in fibrous tissue, in lower cortex most of the tubules show extreme atrophy, the lumina of the remaining tubules are closed by greatly swollen vacuolated cells whose protoplasm is granular and whose nuclei are pyknotic, many casts
60	59	2,600	15	A number of irreg- ular purple scars	No chronic changes scattered casts
61	32	2,000	30	A few small scars	No bands of scarring, no scarred glom- eruli, uniform high grade dilatation and atrophy of tubules, except in outer- most portion of cortex where the cells are swollen and granular, many are vacuolated, many casts
67	28	1,750	29	A few scars	No bands of contraction, uniform marked dilatation and atrophy of tu- bules, glomeruli show no changes, much swelling and desquamation of tubular epithelium, many casts
88	29	1,680	16	Many pitted scars on section, many pale yellow bands seen in medulla	Two small cortical bands of contraction, most of the tubules in the lower cortex show moderate atrophy and dilata- tion, signs of acute parenchymatous injury not marked
77	26	1,477	22	Few deep scars	No bands of contraction, the tubules of lower cortex show nearly uniform dilata- tion and atrophy, in the upper cor- tex are a few small patches of tubular dilatation, most of the remaining tubules are occluded by the swelling of cells, many casts
78	24	1,900	22	No scars	No bands of contraction, the tubules in the lower half of cortex are uniformly dilated and atrophied, in the upper cortex are groups of dilated tubules surrounded by tubules whose lumina are closed by the swelling of the cells, many casts
100	51	3,270	23	Numerous scars	Several bands of contraction, no tubular atrophy, the cells of the tubules of lower cortex show marked injury
108	49	3,530	21	A few small scars	No chronic changes
109	40	2,600	22	Many old scars producing coarsely granular surface	The outermost portion of the cortex is almost changed to fibrous tissue from which a number of irregular bands run down toward the medulla, in the lower cortex, patches of fibrous tissue are seen, there is irregular scarring of glomeruli and patchy atrophy of tu- bules none of these changes can with certainty be attributed to the diet
118	35	1,880	21	Scattered, small scars	Marked uniform atrophy and dilatation of tubules of lower cortex, in the upper cortex, some tubules are atro- phied, the others are lined with gran- ular vacuolated cells, some of whole nuclei do not stain, many casts

\* Animal accidentally killed while withdrawing blood from heart

found in untreated animals. In the remaining three of these twelve rabbits, the nephropathy appeared to be at least in part attributable to conditions unrelated to the diet, and it was impossible to determine how much was caused by the diet and how much was "spontaneous."

The profound effect of the diet on the state of the tubular epithelium is also determined by contrasting the number of cases of dilatation and atrophy of tubules occurring in the control rabbits with the number of cases of such atrophy found among the animals that had eaten the meat-containing diets for twenty-four weeks or



Fig 8—Character of the lesions which are found in some control rabbits. A band of fibrous tissue has caused retraction of the outer surface of the kidney, with scarring of the glomeruli in its path. The sharp separation of the normal tissue in the left half of the field from the portion containing the dilated tubules is clearly seen. The focal character of the tubular dilatation seen in this kidney contrasts strikingly with the diffuse and widespread dilatation of tubules presented in Figures 1, 2, 5 and 6.

more. In making this comparison, no account is taken of the distribution of the tubular dilatation—whether sharply restricted, patchy or diffuse—nor of the presence or absence of other lesions. It is a simple comparison between the percentage of "treated" animals whose kidneys showed tubular atrophy with the percentage of control animals whose kidneys showed tubular atrophy. When this is done it is found that

One of the female rabbits being fed on the diet containing 27 per cent of protein gave birth to a litter of four, sired by a male on the same diet. The observation of these four young rabbits gave further information regarding the injurious effect of the meat-containing diet. The rabbits were born on September 7, when their mother had had the high protein diet for nearly four months. She weaned them on October 10. One of them, weighing 410 gm, died the same day. Necropsy revealed bronchopneumonia. The remaining three took kindly to the high protein diet and gained weight rapidly. Their

TABLE 3—*Nonprotein Nitrogen of the Blood From Meat Eating Rabbits*

No	Diet	Duration, Months	Condition of Animal	State of Kidney	Fasting	Blood N P N Mg per 100 C c
88	Protein 27%	1	Good, blood culture negative	Moderate tubular dilatation and atrophy, urine albumin, few casts	Yes	71
77	Protein 21%	5½	Good, blood culture negative	Tubular atrophy and dilatation, urine much albumin, many casts	Yes	65
78	Protein 21%	5½	Unable to stand, dying	Extreme tubular dilatation and atrophy, bladder urine much albumin, many casts	No	121
67	Protein 27%	6½	Unable to stand, diarrhea blood culture negative	Tubular dilatation and atrophy, bladder urine much albumin, many casts	Yes	114
61	Protein 27%	7	Good	Tubular dilatation and atrophy, urine albumin and few casts	Yes	58
108	Protein 27%	11	Excellent	Tubules not atrophied, urine albumin, no casts	Yes	39
100	Protein 27%	12	Excellent	Tubules not atrophied, urine no albumin, no casts	Yes	60
60	Protein 27%	7	Good	Tubules not atrophied, urine albumin, few casts	Yes	60
		11	Purulent nasal discharge, blood culture negative	Urine same	No	79
		13	Excellent	Bladder urine albumin, rare casts	No	46
147	Protein 36%	5	Excellent	Tubules not atrophied, urine albumin, some casts	Yes	147
138	Protein 36%	8	Excellent	Tubules not atrophied, urine albumin, few casts	No	61

general condition, as evidenced by their plumpness, their shiny coats, their bright eyes and their playfulness was excellent and continued so up to the day of death.

The urine of each of these three rabbits was examined on the third day after weaning. All showed albuminuria, one sediment contained many hyaline and granular casts and a few red blood cells. A few casts, but no red blood cells, were seen in the sediments of the other two. The reaction of these urines was tested with phenolphthalein, which remained colorless, and with methyl red, which gave a pale red, indicating that they were nearly neutral.

75 per cent (twelve out of sixteen) of the meat eating rabbits showed such atrophy, whereas it was present in only 9 per cent (one out of eleven) of the controls

When it is recalled that the nutrition of the controls because of infection was poor (average individual weight, 1,540 gm) and that the general condition of the meat fed animals (average individual weight, 2,375 gm) was excellent, the great difference between 75 per cent and 9 per cent becomes the more significant. It seems clear that the infections to which rabbits are naturally susceptible do not frequently cause dilatation and atrophy of the renal tubules. If one adds to this the facts already brought out, namely, that tubular atrophy in control rabbits is but one part of a focal cicatrizing lesion which also causes scarring of the glomeruli and that tubular atrophy in meat eating rabbits is generalized and unaccompanied by fibrosis or by scarred glomeruli, the conclusion that diets containing 27 per cent or more of protein derived chiefly from meat, when fed for six months or more, are capable of producing high grade dilatation and atrophy of the renal tubules in the rabbit is unavoidable.

Further evidence of the renal injury caused by these high protein diets is obtained from the blood nonprotein nitrogen values.

For control, five adult rabbits were selected at random from the stock cages, fasted twenty-four hours, and blood was then withdrawn from the heart. The following readings were obtained 29.4, 37.5, 39.0, 46.8, 48.0 mg, with an average of 40.5 mg. These rabbits were then fed the high protein diet for eight days. At the end of this period blood was again withdrawn from the heart, omitting the preliminary fast. The object of this second control was to determine what effect, if any, the high level of nitrogen metabolism would have on the nonprotein nitrogen of the blood. The readings were 40.2, 43.8, 48.0, 51.6 and 58.2 mg, with an average of 48.3 mg. These data indicated that slight elevations occurring in the animals that had been on the diet for months might be caused by the excessive nitrogen of the diet rather than by an underlying nephropathy, but that considerable increases in the nonprotein nitrogen of the blood must be caused by something other than the high protein metabolism.

In Table 3 will be found all of the blood nonprotein nitrogen readings obtained from rabbits being fed the high protein diets. It is evident that all but one of these animals were retaining nitrogen waste products and that some of them showed high levels of nonprotein nitrogen in the blood. It was impossible to establish any parallelism between the histologic appearance of the kidneys and the degree of nitrogen retention, nor between the latter and the general condition of the animal.

biologic reactions One of us reported in an earlier paper<sup>4</sup> that the plasma of a rabbit whose sole food was boiled egg white contained no precipitin for pure egg albumin, and that neither the albuminous urine nor the blood serum of a similar rabbit was capable of sensitizing guinea-pigs to egg albumin

This question has been reexamined with the meat containing diet as follows

Dec 7, 1922 Some dry powdered beef was shaken in normal salt solution Two cubic centimeters of the filtrate were then injected intraperitoneally into each of a group of guinea-pigs

Dec 20, 1922 The blood serum from two rabbits that had eaten the diet containing beef to the extent of 36 per cent of protein for weeks, was injected intravenously in 1 cc doses each into four of these guinea-pigs None gave the anaphylactic reaction One cc of a filtrate of the powdered beef was injected intravenously into the remaining three guinea-pigs which had been sensitized to beef protein on Dec 7, 1922 All showed characteristic anaphylactic shock

Here also it was impossible to demonstrate the presence in the blood of the protein of the diet Accordingly, no support was obtained for the surmise that the kidneys were damaged by eliminating foreign protein from the circulation

The experiments of Longcope<sup>5</sup> dealing with the occurrence of renal lesions in animals that had been subjected to anaphylactic shock have already been mentioned as offering a possible explanation of the question under discussion He reported the presence of focal lesions in the kidney (and in some other organs) The individual lesion showed various degrees of parenchymatous injury and a well marked infiltration by small round cells The two most striking features of the lesion were its circumscribed character and the presence in it of many small round cells There is, accordingly, no resemblance between the focal lesions described by Longcope and the diffuse tubular atrophy reported by us The great dissimilarity between the two lesions makes it most unlikely that they could have had the same origin

3 A meat containing diet would, according to current belief, cause the rabbit to secrete an acid urine Since the rabbit's urine is normally alkaline, such a shift in reaction might be attended by cellular damage The urines of the rabbits that were eating the beef protein were generally acid to litmus, although not invariably so, a few of them were neutral It has already been shown in an earlier paper<sup>1</sup> that high protein diets can damage the rabbit's kidney even though the urine remains alkaline In the experiments referred to, one large group of rabbits was fed soy beans Even though the urines were always alkaline, the kidneys of animals that had eaten the soy beans for months presented a well marked chronic nephropathy Another group daily received the following mixture Casein, 30 gm, milk,

These rabbits were found dead on October 24, 29 and 31, respectively, when they were from 6 to 7 weeks old. In no case had the general appearance of the animal on the day preceding death indicated that he was in any way different from a healthy young rabbit. Necropsy revealed no abnormalities other than those relating to kidneys.

The kidneys of the animal that died on the 24th weighed 5 gm (11 per cent of body weight) and on section were found to be pale, wet and totally devoid of markings. No urine was obtained from the bladder.

The kidneys of the animal which died on October 29 weighed 8 gm (16 per cent of body weight). The section surface was engorged and cloudy, and the cut ends of the vessels stood out as bloody points. The bladder urine contained much albumin, many casts and numerous red blood cells.

The kidneys of the rabbit found dead on October 31 weighed 6.5 gm (16 per cent of body weight), the surfaces, on section, were pale, moist and lacking in markings. The bladder urine contained much albumin, many casts and red blood cells.

#### COMMENT

The renal injury which develops in rabbits that are fed a high protein diet may be caused by one or more of a number of abnormal processes.

1 The approximate doubling of the work of the kidney because of the increased nitrogen metabolism comes to mind as such a possibility. But it is well known that normal kidneys merely hypertrophy when required to perform much more than the usual amount of work. Furthermore, one of us reported in a previous paper<sup>4</sup> that simple increase in work brought about by feeding urea to rabbits in amounts sufficient to about double the normal urinary nitrogen for as long as nine months produced no demonstrable renal injury. Simple increase in work does not account for the nephropathy.

2 The excessive ingestion of protein might force its absorption into the blood and the subsequent elimination by the kidney of it or its parenteral digestion products. These substances are believed to be nephrotoxic. This possibility is perhaps emphasized by the work of Longcope,<sup>5</sup> who reported the existence of renal injury in rabbits that had been subjected to anaphylactic shock.

If foreign protein were present in the blood or in the urine, one would expect to be able to demonstrate its presence by means of

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4 Newburgh, L. H. Production of Bright's Disease by Feeding High Protein Diets, *Arch Int Med* **24** 359-377 (Oct) 1919.

5 Longcope, W. T. *J Exper M* **18** 678, 1913.

The microscopic examination of these kidneys revealed no abnormalities except a few casts in the collecting tubules of each kidney

The urinary abnormalities occurring in the oat fed rabbits might or might not have been caused by the acidity of the urine, since a diet of oats alone produces a metabolic disturbance which also might be attended by a disturbance of the kidney. As long ago as 1916, Lewis and Karr<sup>8</sup> stated that "It is now generally accepted that an exclusive cereal diet results in a failure of normal nutrition for most of the common laboratory animals"

There are at present no data available which make it possible to decide whether urinary acidity alone is capable of causing albuminuria and cylinduria. On the other hand, it is clear that even if acid urine does produce albumin and casts, it does not cause the other changes in the kidney which developed in our meat eating rabbits. The nephropathy which we have found in such rabbits may have been in part, but only in part, caused by the prolonged excretion of an acid urine

4 The idea that bacterial decomposition of protein in the intestine gives rise to soluble poisons which are absorbed and eliminated by the kidney with injury to it, is familiar to all students of nephritis. And Harvey<sup>9</sup> claims to have produced chronic nephritis by feeding and injecting parahydroxyphenyl-ethylamin. This amin was isolated by Barger<sup>10</sup> from decomposing meat, and said, by Harvey, to have been found in the alimentary canal of man

The presence of such toxic protein derivatives is said to be indicated by the occurrence of indol in the urine and by an increase in urinary phenol. We have tested the urines of eight rabbits being fed the high protein diet, for the presence of indol with Obermeyer's reagent, and have invariably obtained negative results. In two of these animals the twenty-four hour excretion of phenol in the urine was quantitated by the method of Folin and Denis<sup>11</sup>. Our figures were somewhat lower than those obtained by Folin and Denis from normal rabbits

We, accordingly, obtained no evidence of the excretion of abnormal amounts of bacterial decomposition products. While our examination was inadequate to exclude entirely such a possibility, it left us in the position of having no data which indicated that the disease of the kidney was attributable to the damaging effect of such substances

5 Levene and Van Slyke,<sup>12</sup> in 1912 showed that amino acids are always present in normal urine, and that the total amino acid nitrogen

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8 Lewis, H. B., and Karr, W. G. *J Biol Chem* **28** 17, 1916

9 Harvey, W. H. *J Path & Bacteriol* **16** 95, 1911-1912

10 Barger. *J Physiol* **38** 343, 1909

11 Folin and Denis. *J Biol Chem* **22** 319, 1915

12 Levene and Van Slyke. *J Biol Chem* **12** 301, 1912



25 c c , scraped carrot, 20 gm , sodium bicarbonate, 1 gm , and water, 20 c c The urines remained alkaline, and the kidneys showed severe parenchymatous lesions

Polvogt, McCollum and Simmonds <sup>6</sup> have recently published experiments dealing with the nephropathic effect of high protein diets on the kidney of the rat Their diets were put together in such a way as to make them potentially alkaline and to thus exclude any possible harmful effect resulting from an acid urine The diets were in addition nearly optimal for growth and reproduction In spite of these controls, it was found that "all the rats fed the diets high in protein had lesions of the kidneys of considerable severity"

It is evidently not necessary to invoke the acid producing feature of a high protein diet to explain its nephrotoxic character

Furthermore, it has recently been shown by Hasselmann <sup>7</sup> that the urine of men is less acid when large amounts of meat are eaten than when oats form a considerable portion of the food intake When the diet consisted of 750 gm of meat, 100 gm of fat, 200 gm of bread, 100 gm of potatoes and 1,000 c c of fluid the titratable acidity was 200 in terms of tenth normal alkali and the hydrogen-ion concentration was 6.7 But when 500 gm of oats, 100 gm of fat, 100 gm of meat, 250 gm of bread and 750 c c of fluid were taken the titratable acidity was 350 and the  $p_H$  5.5

Hasselmann states that Magnus-Alstleben has pointed out that the urine of the carnivorous dog is not acid but, on the contrary, shows an alkalinity of an order rarely seen in man, and that Loew found that the urine of the rabbit on an oat diet is acid

We have abundantly confirmed Loew's observation in a group of rabbits that were fed only oats and water for periods ranging from a few months to about ten months, the urines of these rabbits were invariably acid to litmus Such urines always contained albumin and sometimes casts

Two of these rabbits lived on oats and water for about ten months At the end of the first four months the urine of one showed a heavy albuminuria and several casts The other urine gave positive tests for albumin, but no casts were seen The urines obtained the day before the rabbits were killed, each showed a well marked albuminuria, and many casts were seen in one sediment but none in the other sediment The determination (colorimetrically) of the hydrogen-ion concentration of these urines gave readings of 5.9 and 5.5

Necropsy revealed no abnormalities The kidneys weighed 10.7 gm and 11 gm and, except for a few small pits, appeared to be normal

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6 Polvogt, McCollum and Simmonds Bull Johns Hopkins Hosp **34** 168, 1923

7 Hasselmann, C M Klin Wchnschr **2** 122, 1923

for the final picture. We are, however, convinced that the primary injury was a product of the diet, and that if bacteria played any part in causing the lesion they were able to do so only as a result of damage previously worked by the diet.

#### SUMMARY

The majority of rabbits that ate a diet containing 27 per cent or more of protein for six or more months, developed a chronic nephropathy. At least the initial lesion was caused by the products of the diet, since spontaneous infection in the absence of the diet is incapable of causing the disease. The lesion may, in part, have been caused by infection acting on a kidney made susceptible to infection by the diet.

The evidence at hand suggests that the injury caused by the diet is either solely attributable to the excessive excretion of some amino acids or in part to the amino acids and in part to the acid character of the urine. But the acidity of the urine by itself is incapable of causing all of the injury attributable to the diet.

There is no intention on our part of claiming that this nephropathy is the anatomic analogue of human chronic nephritis. On the other hand, the recent work of Polvogt, McCollum and Simmonds<sup>6</sup> "furnishes experimental evidence that the excretion of excessive amounts of the normal end products of protein metabolism may result in anatomical damage to the kidneys of an omnivorous animal when all other requirements for the nutrition of this species are adequately provided for." Furthermore, Squier and Newburgh<sup>16</sup> have published data which, in their opinion, prove that the human kidney may be injured by protein excess. The authors of this paper believe that these experiments on the rabbit bring us one step nearer to an understanding of the etiology of chronic nephritis in man.

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<sup>16</sup> Squier and Newburgh. Renal Irritation in Man from High Protein Diet, *Arch Int Med* **28** 1 (July) 1921.

bears a fairly constant relation to the total urinary nitrogen Van Slyke<sup>13</sup> in a subsequent paper reported that during the digestion of meat the amino acid content of the dog's blood is markedly increased More recently Folin and Berglund<sup>14</sup> have published tables which make it clear that there is an increased elimination of amino acids by the kidneys of man whenever there is an influx of amino acids from the digestive tract sufficient to raise materially the amino acid content of the blood The greatest elimination of amino acid occurred in a subject who took 135 gm of gelatin Before eating the gelatin, the blood contained 5.5 mg of amino acid nitrogen per 100 c c, and the kidney was putting out 10 mg of amino acid nitrogen an hour Two hours later, the blood amino acid nitrogen had risen to 11 mg per 100 c c, and the kidney during the fourth hour following the ingestion of the gelatin put out 96 mg of amino acid nitrogen

It is conceivable that the increased elimination of amino acid which follows the excessive ingestion of protein might not be without effect on the kidneys Some of the amino acids might be nephrotoxic when excreted in unusually large amounts for a long time

Experiments<sup>15</sup> designed to throw some light on this question have progressed far enough to permit a preliminary statement The intravenous injection of an amino acid is regularly followed by a sharp increase in the urinary amino acid The injection of a number of the straight chain amino acids in large amounts has caused no demonstrable injury to the kidney But the intravenous injection of tyrosin and of histidin in very much smaller doses has been regularly followed by the occurrence and often persistence for a number of days of albumin and casts

These results, while suggestive, are not sufficient to make us willing to affirm that high protein diets cause renal damage because they are attended by the excretion of nephrotoxic amino acids

6 The question whether the renal injury was caused by intercurrent infection has already been discussed, and ample evidence has been presented to show that the naturally occurring infections of rabbits do not produce the type of kidney disease which was found in the meat eating animals On the other hand, it is possible that the high protein diet produced a primary renal injury that made the kidneys accessible to the harmful effects of bacteria, which in the absence of such a primary lesion were incapable of causing the lesion Even though the necropsies did not give us the usual evidence of infection, and even though every blood culture was negative, it is true that infection could not with certainty be excluded It is accordingly impossible to state whether bacteria were in part responsible

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13 Van Slyke J Biol Chem **12** 399, 1912

14 Folin and Berglund J Biol Chem **51** 413, 1922

15 Newburgh and Marsh To be published

casts. The hemoglobin content of his blood was 70 per cent. There were 4,000,000 red blood corpuscles and 6,300 white cells. A month later the leukocyte count rose to 11,350. The differential count was normal at all times. There was no eosinophilia. The blood Wassermann reaction was negative. His blood pressure was systolic, 100, diastolic, 80. A blood culture showed streptococci in one bottle, the other bottle remained sterile. Analysis of the stomach contents showed a slight increase in free hydrochloric acid, but the stomach contents were otherwise normal.

*Treatment and Course*—The patient was placed on a soft diet, which caused some improvement in his gastric symptoms.

On January 23, dulness was noticed at both bases with bubbling râles. There were a few wheezing râles over both apices. The liver was not palpable. A general enlargement of the lymph glands was also noted, and the patellar reflexes were still more sluggish. On the whole, he had improved somewhat and was able to get up, but he was never quite well.

On January 26, he said that he had passed bright blood in his stools during the night. Examination at this time showed a puffy swelling on the right side of his face, and also some difficulty in breathing, the breathing being of an asthmatic character. All through the chest there were numerous musical râles. The heart sounds were clear and rapid. On this day, a definite enlargement of the liver was discovered, the lower border of the liver being 5 fingerbreadths below the costal margin.

On January 27, roentgen-ray examination revealed fluid in both pleural cavities, the heart at the upper limit of normal size, and there was a marked enlargement of the liver. On account of evident cardiac insufficiency he was given digitalis in large doses, after which his pulse became somewhat irregular and extrasystoles developed.

On January 31, the patient was much worse, his breathing was labored, there was impaired resonance throughout his chest and marked flatness at both bases. There were many extrasystoles. An accumulation of fluid could be made out in the abdomen and his liver remained markedly enlarged.

On the next day, February 1, the fluid had increased in both pleurae and in the abdomen. On this day there was a slight rise in temperature.

On February 4, a slight edema of the lower extremities was observed. His pulse was distinctly irregular, and edema of the right lower eyelid had developed.

On February 5, weakness was noticed in the seventh cranial nerve on the right side and ptosis of the left eyelid. The signs of cardiac decompensation continued.

There was a short period of improvement from February 7 to February 12, and on February 12 his pulse was regular, slow and of low tension.

On February 18, the accumulation of fluid in his pleural cavities had apparently disappeared.

On February 22, he developed edema of the right hand and of both feet. His pulse was 100, regular.

On February 28, he was again in marked distress with dyspnea, wheezing respiration and much sweating.

On March 1, he was much worse, his pulse was very rapid, there were many extrasystoles, and his respiratory distress was pronounced.

He died quietly on March 2 at 3:30 a. m.

During the course of his illness at the hospital his temperature was normal or subnormal with an occasional rise to 100 F. There was much sweating, especially during the periods of exacerbation of his illness. The pulse rate ranged between 70 and 110, but was usually high. The respiration rate varied between 20 and 30. Urinalysis from time to time showed a small amount of albumin and a few hyaline and granular casts. His blood pressure was consistently low. The fluid removed from his chest contained much albumin, a considerable number of leukocytes, mostly polymorphonuclears (about 70 per

# PERIARTERITIS ACUTA NODOSA

W OPHULS, M D

SAN FRANCISCO

About seventy observations of periarteritis nodosa have been recorded in medical literature. The disease is still so obscure however that every new case reported may assist in its final elucidation. I shall discuss briefly a case observed in the Stanford Medical Service at the San Francisco Hospital.

## REPORT OF A CASE

*History*—I G, a Persian janitor, aged 38, was admitted to the San Francisco Hospital on Dec 12, 1922, complaining of severe pain in the stomach one or two hours after eating, without local tenderness, followed frequently by eructations of gas, also of occasional night sweats. These symptoms had commenced in July, 1922. One week after the onset of these symptoms his appendix had been removed, which gave him temporary relief. He remained at the hospital for about ten days. The pain in his stomach returned, however, and persisted at varying intervals until his entrance to the San Francisco Hospital five months later. He was nauseated at times but had never vomited. Recently he had had nocturia three or four times. The patient did not speak English very well, and for that reason it was difficult to obtain an accurate history, but so far as could be made out, he had always been well until the appearance of these symptoms. He denied venereal and other severe infections. He had been injured several times during the Great War, but not severely. He did not use liquor or tobacco. He had been married for eighteen years. He had three children, all of them well, the oldest one being 17. He had lived in Persia until six years ago when he came to the United States. His average weight had been 150 pounds (68 kg), but since he had been ill he had lost weight until his weight at entrance to the hospital was 115 pounds (52.1 kg).

*Physical Examination*—The patient was undernourished. He coughed occasionally without raising any sputum. His pupils were slightly irregular and reacted fairly well to light and accommodation. There was a subconjunctival hemorrhage in his right eye. His tonsils were moderately enlarged, and in the crypts there was some grumous material. Examination of the lungs did not reveal anything abnormal. The heart seemed to be within normal limits. The heart sounds were loud and snapping, the second pulmonic tone was greatly accentuated and rough. No definite murmurs were heard. A careful examination of the abdomen did not reveal any abnormalities. There was no spasticity or tenderness anywhere. There were no paralyses. The patient did not complain of any abnormal sensations. The patellar reflex was sluggish, especially on the right side. Two blisters were found in the skin on the inner side of the right knee.

A fluoroscopic examination revealed considerable grayness at both apexes and fixation of the left diaphragm. A careful examination of the nose by a specialist revealed some irregularity of the septum, a good breathing space and no discharge. Urinalysis revealed little albumin and occasional hyaline and granular

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\*From the Department of Pathology, Standard University Medical School

The right peribronchial lymph glands were large. Many grayish white nodules were seen in the pleura at the right apex. There was also present a superficial scar 1.5 cm in diameter. The right lung otherwise resembled the left one. The tissue at both bases was quite firm.

A few old adhesions were found about the spleen. Its capsule was slightly thickened. The splenic artery was normal. The spleen measured 13.5 by 8.5 by 4 cm. The markings were distinct.

The left suprarenal body was small, otherwise normal.

The left kidney was large. The capsule stripped easily. It measured 15 by 6 by 3.5 cm. The cortex was dark purple and showed a large number of grayish white opaque spots. On the cut surface the cortex was quite wide and full of similar spots. The pyramids showed a marked passive congestion.

The right suprarenal was like the left one. The right kidney was similar to the left one.

The bladder, the prostate, the seminal vesicles and the rectum were normal.

Easily broken adhesions were found in the region of the gallbladder, extending quite a distance into the surrounding area. The duodenum and its contents were normal. The bile duct was patent.

The stomach was much distended. It contained grayish fluid and many flakes of mucus. Some adhesions were present between the stomach and pancreas. The mucous membrane of the stomach was somewhat congested. It was covered with a thick layer of mucus. The fundus showed postmortem digestion.

The lymph glands at the liver hilus were enlarged and smooth. Their cut surface was dark red.

The pancreas was normal.

The abdominal arteries were normal.

The gallbladder was filled with thick viscid bile.

The liver measured 28 by 24 by 9 cm. In and underneath the capsule there were irregular white strands apparently following the course of the larger blood vessels. The cut surface showed an extreme passive congestion and a definite thickening of the connective tissue about the larger blood vessels. There was also a marked cyanosis of the centers of the lobules and evidence of beginning cyanotic atrophy.

The appendix had been removed. No adhesions were seen at the point of operation.

No intestinal parasites were found. The mucous membrane of the lower ileum and of the large intestine showed a marked passive congestion. It was otherwise normal. The mesenteric lymph glands were slightly enlarged, congested and grayish red. The retroperitoneal glands were in the same condition. No signs of tuberculosis were discovered in them.

The thoracic and abdominal aorta was normal.

The skull was distinctly asymmetric, the skull cap being flatter in the right occipital region. It was otherwise normal. The longitudinal sinus contained fluid blood. The pia mater on both sides was slightly congested. The brain showed an asymmetry similar to that of the skull. The large arteries at the base of the brain were normal. The large venous sinuses were normal. There were no visible lesions in the motor cortex. The brain tissue was hyperemic and edematous throughout. No focal lesions were found.

*Anatomic Diagnosis*—The anatomic diagnosis was (1) acute nodular periarteritis, (2) subacute myocarditis of the left ventricle with hypertrophy and dilatation of the right ventricle, (3) emphysema, (4) healed apical tuberculosis of the lungs, (5) subacute nodular pericarditis, (6) subacute pleurisy, (7) subacute peritonitis, (8) subacute nephritis and (9) healed appendectomy.

*Histological Examination*—Sections of the lung showed an involvement of the small arteries, of the veins, of the pleura and the interlobular septums, of the bronchial tubes and of the pulmonary tissue proper. The lesions in the small

cent) No eosinophils were noted On February 1, some diplococci were noticed in a smear from the pleural fluid, but a culture made at the same time did not show any growth His sputum, of which there was little, was examined several times for tubercle bacilli, always with a negative result

The findings and the course of the disease were so unusual that the clinicians refused to make a diagnosis

*Necropsy*—Necropsy was performed on March 2, 1923 The body was that of a strongly built, fairly well nourished and muscular man of about 40 years His pupils were widely dilated and equal The face and neck showed marked cyanosis The left axillary and the femoral lymph glands on both sides were distinctly enlarged Many purple spots from 2 to 10 mm in diameter were seen in the skin on the inside of the left thigh Both legs showed a moderate edema A scar was found in front of the right tibia, which was moderately firmly attached to the bone (healed war wound) Two small pigmented halos were seen in the skin on the inside of the right knee The scrotum was slightly edematous The finger tips were cyanotic The veins about the anus were markedly dilated The complexion was very dark (Persian) The skin was dark all over the body

A scar from a healed laparotomy was seen on the right side in the appendicial region (appendectomy) A recent small superficial incision was found in the midline about half way between the umbilicus and the pubic region

The abdomen was distended and tense with gas The omentum was slightly adherent to the anterior abdominal wall The subcutaneous fat was atrophied The abdominal muscles were pale and poorly developed

The liver projected 4 fingerbreadths in the right mammillary line and in the left lobe 5 fingerbreadths below the xyphoid process

The lower border of the stomach was at the umbilicus

The omentum showed some small irregular scars

The peritoneum showed a dark purplish discoloration It was smooth, glistening and moist, 50 cc of blood stained fluid were found in the rectovesical pouch

The level of the diaphragm on the left side was at the fourth rib, on the right side at the fifth rib

The chest was strongly arched, almost barrel shaped, and symmetric

A few easily broken adhesions were found in the lower part of the left pleura About 100 cc of clear fluid were present at the left base Few easily broken adhesions were noticed in the upper part of the right pleura, and about 150 cc of clear fluid in the lower part

In the pericardium there were 200 cc of slightly turbid yellow fluid Both layers of the pericardium were irregularly congested and covered with a thin layer of fibrin In the inflamed pericardium at the base of the heart there were some just visible grayish nodules A large milk spot was found over the right ventricle

The heart was slightly enlarged The right side was dilated Dark fluid blood filled the pulmonary artery The right ventricle and the right auricle were distinctly dilated The wall of the right ventricle was firm, measuring 4 mm on cross-section Many just visible grayish nodules were seen in the pericardium over the pulmonary artery The pericardium along the course of the coronaries and their branches were rather white and thick, but there were no nodules at these points The left ventricle was not dilated It measured 12 mm on cross-section The base of the aorta and the coronary arteries were normal The heart muscle on the left side was firm and full of grayish white, small irregular spots The valves of the heart were normal

A large amount of mucopurulent material was found in the left bronchus The left pleura was smooth and glistening The left lung was large and emphysematous The bronchial tubes were congested The bronchi in the lower lobe contained much mucopurulent material The peribronchial lymph nodes were enlarged, moist and contained a few grayish spots The posterior lower parts of the left lung were congested and edematous



Fig 2—Smaller branch of pulmonary artery showing more acute changes, with coagulated exudate in intima



Fig 3—Section of pleura with marked subacute pleurisy



arteries (Fig 1) consisted in a heavy infiltration of the peripheral layers of the adventitia with leukocytes, mostly with eosinophils, but there were also a few lymphocytes and plasma cells. In the central parts of the adventitia the leukocytes were much less numerous. Here there were mostly fusiform or irregularly shaped cells which contained large clear nuclei. The general appearance of these cells was that of fibroblasts. The muscular layer was generally fairly well preserved, but there were places in which the muscle cells were more or less vacuolated and in which the media was invaded both by the eosinophils and the large proliferating cells of the adventitia. The changes in the adventitia were not localized in the shape of nodules but were quite diffuse, although there were stretches of the small arteries which were quite normal. There were marked changes in the intima consisting of a marked cellular thickening of this coat apparently corresponding more or less closely to the damaged parts of the media. The cells in the intima also had the characteristics of fibroblasts, and there were delicate fibrils between them. Where the process was recent



Fig 1—Small branch of pulmonary artery showing lesions of periarteritis

some of these cells may have been derived from the endothelium. In the thickened intima there were few eosinophils which seemed to come from the adventitia. In some places (Fig 2) the intima contained some homogeneous material which stained a bright red with eosin (evidently coagulated plasma, as was shown by irregular masses of fibrin in it). It was present in narrow bands, but sometimes it occurred in large quantities practically occluding the lumen. It could be demonstrated, however, in most places that this material was still underneath the endothelium. The material contained more or less degenerated leukocytes. Even where the lumen was much narrowed it was still free and filled with normal blood. In other vessels there was evidence of recent thrombosis. The intimal changes were not so diffuse as those in the adventitia, but they also were not distinctly nodular. The media even at the most severely altered places remained fairly intact. There was no evidence of aneurysmic dilatation of any of the affected arteries.

pneumonic consolidation in which the air spaces were filled with eosinophils, large mononuclear cells, lymphocytes and red blood corpuscles. The air spaces in these areas contained considerable fibrin. Even in such places no bacteria could be demonstrated.

Section of a peribronchial lymph gland contained a moderate amount of coal pigment. The cells in the proliferative centers were swollen and more or less degenerated. The centers contained a few neutrophilic leukocytes and in the periphery deposits of fibrin, some of which were quite hyaline. The lymph spaces were dilated and filled with red blood corpuscles, many eosinophils, a few lymphocytes and large mononuclear cells. The lymph-adenoid tissue was full of plasma cells and was diffusely infiltrated with eosinophils. The capsule showed perivascular infiltrations with eosinophils and plasma cells which extended into the loose connective tissue on the outside. A large artery



Fig 5—Two arterioles in lung occluded by disease and inflammatory infiltration of pulmonary tissue

near the lymph gland showed characteristic lesions: infiltration with plasma cells and eosinophils in the peripheral adventitia, proliferation of connective tissue in the central adventitia with invasion of the damaged media, marked cellular thickening of the intima with moderate infiltration with eosinophils, swelling, partial detachment and proliferation of endothelial cells with a collection of leukocytes and red cells underneath the partly detached endothelium, infiltration of the intima with uncoagulated plasma and fibrin.

Other lymph glands showed similar lesions. The large lymphatic vessels near them were distended with lymph in which there were many eosinophils, fewer lymphocytes and plasma cells and few neutrophilic leukocytes.

The pulp of the spleen was diffusely infiltrated with eosinophilic leukocytes, the proliferative centers in the malpighian bodies showed the same lesions as those in the ones of the lymph glands. The arterial lesions were not marked.

Many of the small veins showed a heavy infiltration of their adventitia with leukocytes (mostly eosinophils). In a few of them the endothelium was distinctly swollen and evidently proliferating.

The perivascular lymphatics were distended with leukocytes, mostly eosinophils.

The large arteries and large veins were normal, but some of them contained recent thrombus.

The pleura (Fig 3) and interlobular septums were heavily infiltrated with eosinophil leukocytes, and the blood vessels in them were very much congested. Where the endothelial layer of the pleura was still preserved, the endothelial cells were distinctly swollen. On the surface and between the endothelial cells there were many diplococci in most places, although some were free from

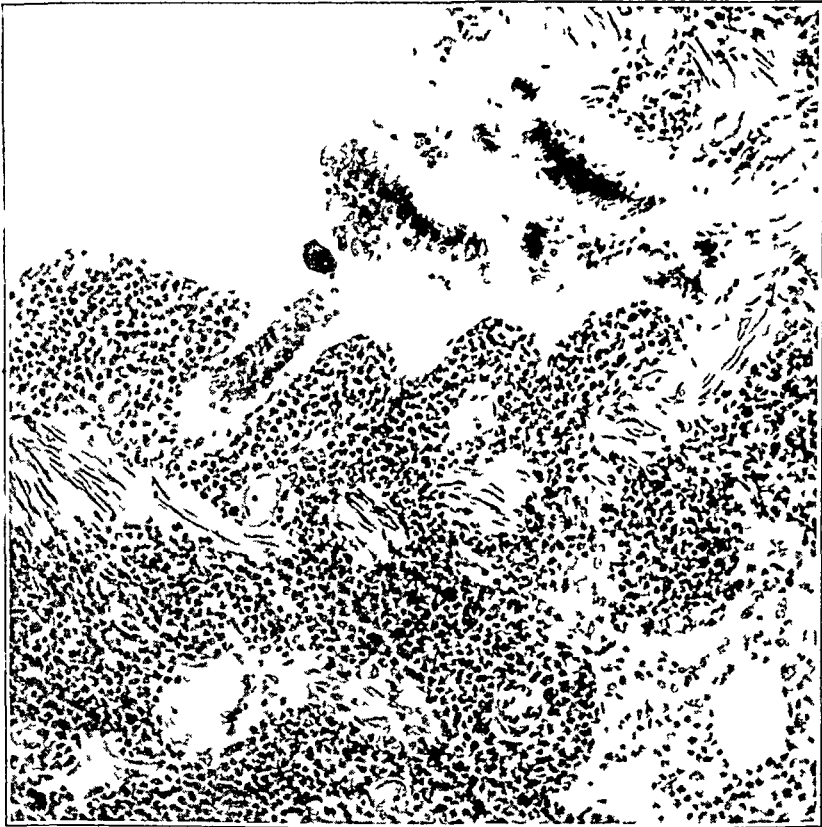


Fig 4—Section of bronchus with tremendous infiltration of mucous membrane with eosinophils

them (contaminations). There were no deposits on the surface of the pleura. The top layer of the pleura was sometimes excessively infiltrated with leukocytes. The lesions in the pleura were quite diffuse and had no direct relation to the blood vessels.

The wall of the bronchi (Fig 4) were diffusely and heavily infiltrated with eosinophils. There were also a few lymphocytes and some fibroblasts. The change was most marked in the mucous membrane and in the loose peribronchial connective tissue. It seemed to extend diffusely from the largest bronchi down to the respiratory bronchioles. Some of the bronchial arteries show marked periarteritis and endarteritis with partial destruction of the media.

The pulmonary tissue proper (Fig 5) showed a diffuse infiltration with eosinophils. This in places led to the formation of small areas of broncho-

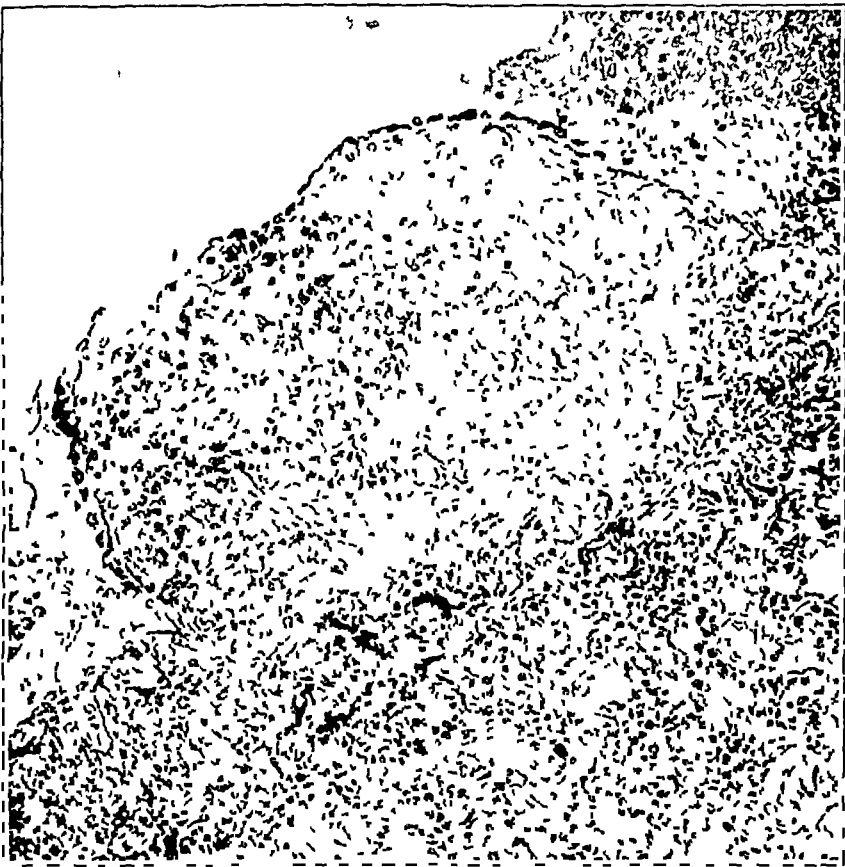


Fig 7—Nodular subacute pericarditis



Fig 8—Granulomatous nodule in branch of renal artery with destruction of media

The adventitia of a few small arteries was thickened and fibrous, and there were a few eosinophils in the new fibrous tissue. The media and the intima of these arteries were of normal appearance. A small amount of haematogenous pigment was found in the pulp.

Some of the larger arteries of the heart showed characteristic changes: heavy infiltration of the adventitia with eosinophils, lymphocytes and plasma cells, cellular proliferation of inner parts of adventitia with often deep invasion of the not severely damaged muscle by cellular new connective tissue with many capillaries in which there were many leukocytes, infiltration of the intima with eosinophils and cellular proliferation, swelling and partial detachment of the endothelium. Similar lesions were also found in the walls of some of the veins. The perivascular connective tissue all through the heart muscle was heavily infiltrated with leukocytes and showed a marked cellular proliferation, and from there the process extended quite diffusely into

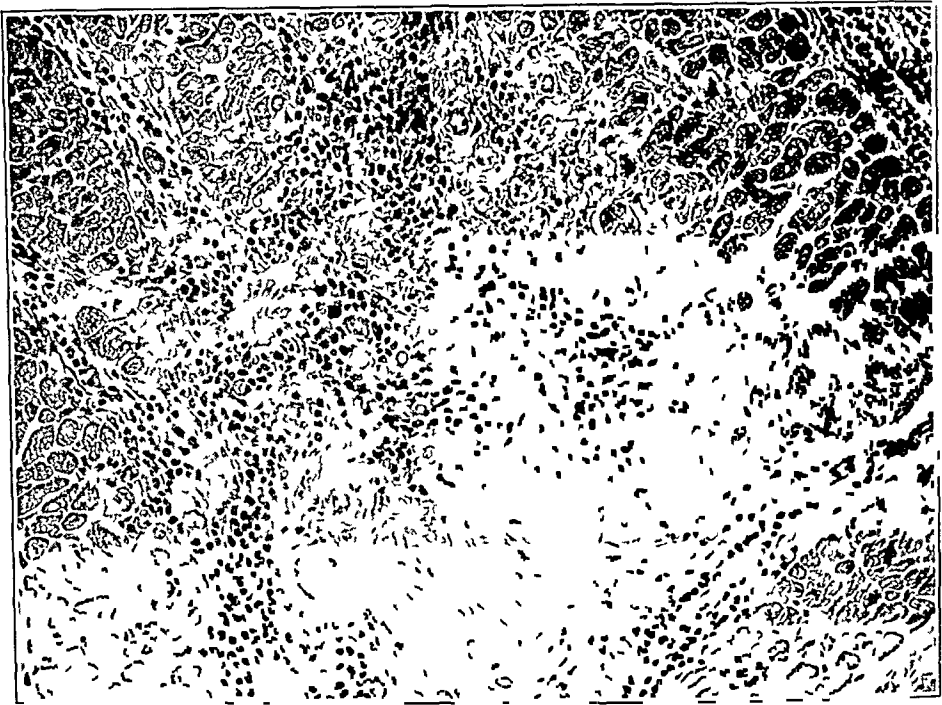


Fig 6—Marked subacute interstitial myocarditis

the musculature (Fig 6). This was especially noticeable on the right side. Here there were even considerable collections of eosinophils and lymphocytic cells between the muscle and the endocardium. In the diseased muscle there were some fairly large cellular scars. The most remarkable lesions were found in the pericardium (Fig 7) where, in addition to the characteristic changes in many arteries and some veins, there was a diffuse infiltration of the fat with leukocytes and a nodular proliferation of the top layers which was especially marked on the right side. These nodules arose from the connective tissue of the surface layer of the pericardium with a broad base, and projected over the surface. They were of about the size of tubercles, and consisted of vascular young connective tissue full of eosinophils and plasma cells. Their surface was covered with swollen endothelium, and in them were numerous small glandlike crypts lined with cuboid endothelial cells. The endothelial cells on the surface of the pericardium were swollen everywhere. In some places the surface was contaminated with bacteria of various kinds, but otherwise no bacteria could be found in the sections.

cells of the convoluted tubules were swollen and partly desquamated, in places they had formed large multinuclear giant cells by fusion. The glomeruli were congested, but even in the areas with interstitial inflammation they were otherwise normal. Many of the small veins were surrounded by heavy masses of leukocytes. The arterioles did not seem to participate in the process. The infiltration with eosinophils and lymphocytic cells in places extended far down into the pyramids. No bacteria were found in the section in spite of careful search.

The lesions in the arteries of the liver (Fig 10) were practically identical with those in the kidney. The destruction of the arterial wall was often even more complete, the tendency of the granulation tissue to arrange itself into cellular nodules even more marked. The tendency to proliferation of the vascular endothelium in these nodules was also pronounced. In the center



Fig 10—Several granulomatous nodules in wall of branch of hepatic artery

of some of the obliterated arteries new lumina had developed from the dilated capillaries. In the proliferating connective tissue there were many eosinophils, and in some places coagulated fluid was seen. The perivascular connective tissue was heavily infiltrated with eosinophils and plasma cells and often greatly thickened, but there was little evidence of an invasion of the liver tissue proper. The liver cells were normal, except that the central capillaries were greatly dilated and the liver cells between them distinctly atrophied. In the capsule of the liver some of the small arteries were distinctly diseased, and there was a moderate diffuse infiltration with eosinophils and plasma cells. No nodules were seen. In these sections also no bacteria were discovered.

In the pancreas some of the larger arteries were badly diseased, resembling very much those found in the heart. There was a moderate infiltration of the interlobular connective tissue with eosinophils and plasma cells and a similar quite heavy infiltration about some of the ducts. Even between the acini and

In an artery of medium size the muscle cells in some places were more or less vacuolated, the intima showed a cellular thickening and contained a moderate number of eosinophils. The arterioles in the surrounding fat showed a marked infiltration of the wall, with large fibroblasts with nearly complete obliteration of the lumen. The latter lesions were somewhat nodular in character.

The changes in the medium sized arteries of the kidney were severe (Fig 8), the infiltration of the adventitia with eosinophils and lymphocytic cells was marked, the proliferation of the inner layer pronounced, the muscle was actually necrotic and hyaline in a few spots, in others distinctly vacuolated and in places completely destroyed by the invasion of granulation tissue from the adventitia. The intima contained some eosinophils and showed a marked cellular proliferation, the endothelium was swollen. In some places the



Fig 9—Diffuse subacute interstitial nephritis

thickened intima was full of hyaline material. The connective tissue proliferation which arose from the adventitia in some places was distinctly nodular. The nodules were cellular, contained blood vessels, were about the size of tubercles and lay partly in the inner layer of the adventitia, partly in the destroyed media. The nodules consisted of unusually large fibroblasts and contained some eosinophils and lymphocytic cells. None of them showed evidence of caseation. The endothelial cells of the blood vessels were often very much swollen, but no giant cells were found. In some of the small arteries the wall was entirely destroyed by the granulation tissue, the lumen was closed, or new lumina had been established by capillary dilatation in the new connective tissue. From the perivascular connective tissue granulation tissue heavily infiltrated with eosinophils and plasma cells radiated far out into the kidney tissue proper (Fig 9), filling the spaces between the tubules and causing their collapse. In the tubules in these areas one often found accumulations of more or less degenerated eosinophils or hyaline casts. The epithelial

few polymorphonuclear leukocytes, many small gram-positive diplococci and short chains and a few other bacteria. The stomach at necropsy was found perforated as a result of postmortem digestion. Cultures from the peritoneum on slant agar and beef tea did not show any growth.

A smear of a testicle showed many large poorly staining cells, few lymphocytes and few polymorphonuclear leukocytes, no bacteria were found in spite of careful search. Cultures on the same mediums did not show any growth.

Smears stained with Giemsa showed the same results, no spirochetes or other parasites were seen in any of the smears in spite of good stain and brilliant illumination.

Rabbit 5 was killed on May 8, 1923. No gross lesions were discovered at necropsy, except a moderate probably spontaneous cirrhosis of the liver. Sections from various organs did not reveal any characteristic lesions. In the liver the periportal connective tissue showed a marked round cell infiltration, which naturally led to some round cell infiltration of the wall of the blood vessels in it. Similarly some of the blood vessels in the lungs showed a few lymphocytic cells in the adventitia, but the changes were so little characteristic that the result must be considered negative. Cultures of the tissues of the rabbit were made on a great variety of mediums, with negative results.

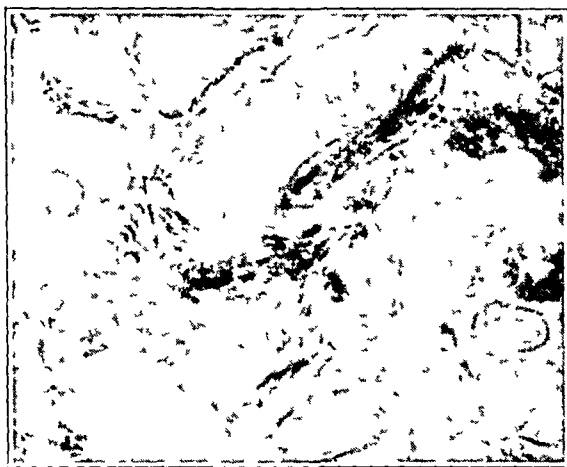


Fig. 11—Small silver precipitates in cells of inner adventitia of diseased artery. High power magnification.

Several rabbits were injected intravenously with the fluid obtained from aseptically ground up organs filtered and unfiltered, but they promptly died, probably of fibrin ferment poisoning. Two more injected intraperitoneally with filtered and unfiltered tissue fluid did not develop any lesions.

Sections from practically all organs in this case were stained with the Giemsa stain and carefully searched for bacteria, with negative results except for the contaminations noted in the protocols of the histologic examination.

Pieces from lungs and pleura, the spleen, the liver, the kidneys, the heart and pericardium were stained according to the Levaditi method. No spirochetes could be detected in them in spite of careful search. In the cell bodies of the proliferating cells in the inner layer of the adventitia in various organs minute silver deposits were found in the shape of small round or slightly rod shaped objects, which are shown in Figure 11. Whether they have any particular significance could not be determined. It might be well to look for them in future cases. They occur in the place that is suspected by many to harbor the initial infection, but silver deposits in impregnated specimens are notoriously misleading.



in the islands of Langerhans eosinophils were found singly or in groups. The glandular tissue was otherwise quite normal. No bacteria were found in these sections.

The prostatic glands contained many amylaceous bodies. They were otherwise normal. In the prostate, and especially in the muscle surrounding it in the periphery, there were many large irregular areas of infiltration with lymphocytes, plasma cells and eosinophils. Some of the arteries showed a complete replacement of the wall with dense rather cellular fibrous tissue with almost complete obliteration of the lumen. The endothelial cells were swollen. In the peripheral parts of the adventitia there were many eosinophils. A sympathetic ganglion near these blood vessels was diffusely infiltrated with eosinophils. A small vein was also surrounded by numerous eosinophilic leukocytes.

The mucous membrane of the stomach was moderately but diffusely infiltrated with lymphocytes, plasma cells and eosinophilic leukocytes. The glands were normal. In the submucosa many eosinophils were found in the immediate vicinity of both arteries and veins, but the vessels themselves were not altered. The connective tissue between the bundles of the muscularis and about the blood vessels of the muscular coat was also full of eosinophils. The blood vessels themselves were normal, except a few larger arteries which show marked changes. Similarly the peritoneum contained some eosinophils, and in one place there was a small projecting vascular nodule full of eosinophils.

The lesions in the mucosa, submucosa, muscle and peritoneum of the small intestine were very much like those in the stomach. The peritoneum was more seriously involved, there were more lymphocytes and plasma cells, and the vascular nodules on the surface were more numerous. The peritoneal endothelium was not preserved.

The eosinophils in the mucous membrane of the colon were quite numerous. There was little change in the submucosa. In the muscle and in the peritoneal tissue arteries were found in which cellular fibrous tissue had developed both in the adventitia and the intima, accompanied by the usual infiltration with leukocytes.

Many muscle fibers of the abdominal musculature showed evidence of waxy (hyaline) degeneration, the endomysium and perimysium were moderately infiltrated with eosinophils. In few small arteries the walls were replaced by cellular fibrous tissue, and the lumina were practically obliterated. In the intermuscular fat there were many eosinophilic leukocytes and some lymphocytes.

The brain tissue and the blood vessels in it and in the pia were normal except for the presence of a few lymphocytes in the perivascular lymphatics here and there.

*Bacteriologic Examination*—Smears from the pericardium stained with Gram stain or Giemsa stain showed many red blood corpuscles, many endothelial cells, many small and large lymphocytes, few polymorphonuclear neutrophilic leukocytes, some large phagocytes containing degenerated red cells and coarse brown pigment granules and a few uncertain diplococci. No other bacteria were found. Smears from the spleen showed normal cells, no bacteria. Smears from the bone marrow showed many eosinophilic myelocytes, otherwise normal cells. No bacteria were found. Smears from the left renal pelvis showed many epithelial cells, few leukocytes, no bacteria.

Rabbit 5 was inoculated in the right testicle, the right ear and intraperitoneally with mixed scrapings from the liver and kidney lesions in beef tea on March 5, 1923.

Guinea-pig 6 was inoculated into the right testicle, subcutaneous tissue on the belly and intraperitoneally with the same material on March 5, 1923. Guinea-pig 6 died on March 7, 1923, at noon. Necropsy, on March 7, 1923, 5 p. m., revealed a distended belly, an injected peritoneum, an intestine distended with gas, very little serous exudate. The right testicle was swollen and congested. Smears of the peritoneum showed a few red blood corpuscles, a

6 The extensive involvement of the veins in many organs This also has been noted a few times only<sup>6</sup>

7 The diffuse infiltration of lymph glands and spleen with eosinophils This is mentioned by Lamb in both of his cases and therefore may have been overlooked by other investigators

8 The finding of numerous eosinophils scattered all through the mucous membrane of the gastro-intestinal tract This, so far as I know, is a unique observation, but this lesion may be quite common, as it is also likely to be overlooked

9 The remarkable extension of the process from the perivascular connective tissue into myocardium and renal tissue This has been fairly frequently seen in the case of the myocardium, but although subacute nephritis has also been observed quite often, it usually was of the nature of an apparently independent hematogenous glomerulonephritis In our case the lesions were local extensions of the inflammatory process through the interstitial tissue, and the glomeruli were not involved or only secondarily More limited foci of such interstitial subacute inflammation were also discovered in sections of the pancreas, prostate and muscle

10 The comparative absence of severe lesions in the arteries of the gastro-intestinal tract

#### PATHOLOGY OF PERIARTERITIS NODOSA

In spite of the obvious difficulties on account of the complexity of the disease, I shall attempt to give a brief summary of its pathology

The clinical symptoms are always obscure, so much so that the clinical diagnosis has been made only when material from the diseased arteries was obtained by biopsy, usually from subcutaneous nodules or in one case<sup>7</sup> from the mesentery in the course of a laparotomy Unfortunately, these subcutaneous nodules are present only in a small minority of the cases

The disease attacks mostly young persons who apparently are in the best of health The youngest victim of it was a child of 2½ years old, but it has been observed several times in persons over 50, and in one case in a man of 62 Among those afflicted the male sex predominates in a proportion of about 5:1 The average age was 31 in a long series of male cases and in a much smaller series of cases in women

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6 Beitzke *Präparate eines Falles von Periarteritis nodosa*, Berl klin Wchnschr **65** 1381, 1908 *Ueber einen Fall von Periarteritis nodosa*, Virchows Arch f path Anat **199** 214, 1910 Von Haun *Pathohistologische und experimentelle Untersuchungen über Periarteritis nodosa* Virchows Arch f path Anat **227** 90, 1920

7 Baehr *Periarteritis nodosa*, Proc New York Path Soc **19** 131, 1919 Manges and Baehr *Periarteritis nodosa*, Am J M Sc **162** 162, 1921

## SPECIAL FEATURES IN AUTHOR'S CASE

1 The almost complete absence of any gross nodules in connection with the disease of the arteries and the complete absence of the development of aneurysms. This, however, has also been noticed in other early cases<sup>1</sup>. The lack of aneurysms in this case is probably to be explained by the comparative absence of extensive medial destruction and the massive development of fibrous tissue in those places in which the media is completely destroyed. Microscopic granulomatous nodules in the inner adventitia extending into the media with destruction of the latter were found in the sections of kidney and liver.

2 The marked involvement of the serous membranes with development of just visible granulomatous nodules on the surface of pericardium and peritoneum. The occurrence of pleurisy, pericarditis and peritonitis in connection with the disease is mentioned in several cases in the literature, the latter, however, was usually due to perforation of intestinal ulcers. The granulomatous nodules I have not found mentioned in any report except in a recent one of Fishberg,<sup>2</sup> who describes in his case in the pericardium flat white thickenings and fine nodules without, however, giving a more detailed description of them.

3 The diffuse infiltration of the bronchial tubes with eosinophilic leukocytes similar to that which is commonly observed in asthma, with asthmatic symptoms. This seems to be an unusual occurrence in periarteritis nodosa. Lamb<sup>3</sup> reports that in one of his cases the patient had suffered from asthma of increasing severity, but this is the only reference to this condition which I have been able to discover.

4 The extensive involvement of the smaller branches of the pulmonary artery. The bronchial arteries have been found diseased in quite a few cases, but the pulmonary arteries rarely<sup>4</sup> (in Walter's case the lesions were purely microscopic).

5 The infiltration of the pulmonary tissue itself with the development of small pneumonic foci full of eosinophils in which no bacteria could be demonstrated. Monckeberg<sup>5</sup> is the only one who describes similar lesions of the lung.

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1 Hart. Ueber Mesoperiarteritis (Periarteritis nodosa), Berl klin Wchnschr **45** 1305, 1908. Kunne über Mesoperiarteritis (Periarteritis nodosa), Frankfurt Ztschr f Path **5** 105, 1910. Fishberg. Zur Kenntniss der Periarteritis nodosa, imb Histopathogenese, Virchows Arch f path Anat **240** 283, 1923.

2 Fishberg. Footnote 1.

3 Lamb. Periarteritis nodosa—a Clinical and Pathological Review of This Disease with Report of Two Cases, Arch Int Med **14** 481, 1914.

4 Monckeberg. Ueber Periarteritis nodosa, Ziegler's Beitr **38** 101, 1905. Kroetz. Zur Klinik der Periarteritis nodosa, Deutsch Arch f klin Med **135** 311, 1921. Walter. Beitrag zur Histopathogenese der Periarteritis nodosa, Frankfurt Ztschr f Path **25** 306, 1921.

5 Monckeberg. Footnote 4.

necrotic infarcts The disease may also extend directly into the kidney tissue, causing a subacute interstitial nephritis, as in my case Commonly also it is associated with an apparently hematogenous nephritis of the general type of any acute or subacute glomerulonephritis Changes in the composition of the urine are therefore rarely missing, and in some cases death has occurred from uremia If the aneurysms are situated rather superficially underneath the capsule, they may rupture, causing large subcapsular hemorrhages These hemorrhages may cause death by acute anemia<sup>11</sup> The lesions in the arteries may be largely limited to the kidneys, as in Fishberg's case,<sup>2</sup> or may extend down into renal pelvis ureters<sup>12</sup> and bladder

In few cases an involvement of the arteries of the generative organs has been described (prostate, seminal vesicles, testes, uterus) In the testes the arterial lesions may produce hemorrhagic necrosis and cause swelling and tenderness in this organ<sup>13</sup>

The arteries of the spleen are often diseased and exhibit the same lesions as those in the kidneys, with the frequent production of more or less extensive and numerous infarcts in the splenic tissue The diffuse infiltration of the pulp of the spleen and of the usually moderately enlarged lymph glands with eosinophils has already been alluded to In the more acute cases a typical enlargement and softening of the spleen may be present like that which is observed in other acute infections

In the liver the most characteristic change is the development of peculiar white strands of fibrous tissue which follow the course of the diseased arteries but do not usually penetrate deeply into the liver tissue proper The arteries usually show nodular thickenings and multiple aneurysms Extensive thromboses are frequently observed in them and may lead to the formation of infarct-like areas in the hepatic tissue The larger arteries at the hilus of the liver may be involved, and in one case<sup>14</sup> death was due to rupture of an aneurysm of the hepatic artery into the peritoneal cavity

The characteristic changes may also occur in the arteries of the gallbladder and here may lead to hemorrhages, necroses and ulceration in the wall of this organ, causing the appearance of symptoms of acute cholecystitis

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11 Bloch, Vera Ueber Periarteritis nodosa, Inaug Diss Zurich, 1913  
Walter Beitrag zur Histopathogenese der Periarteritis nodosa, Frankfurt  
Ztschr f Path **25** 306, 1921 Harris and Friedrichs The Experimental Pro-  
duction of Periarteritis nodosa in the Rabbit with Consideration of the Specific  
Causal Excitant, J Exper M **36** 219, 1922 Mertens Ueber Periarteritis  
nodosa mit Massenblutung im Nierenlager, Klin Wchnschr **1** 1844, 1922

12 Oberndorfer Ein Fall von Periarteritis nodosa, Munchen med  
Wchnschr **54** 2618, 1907 Bomhard Periarteritis nodosa als Folge einer  
Staphylokokkensepsis nach Angina, Virchows Arch f path Anat **192** 305, 1908

13 Monckeberg Footnote 4

14 Klotz Periarteritis nodosa, J Med Res **37** 1, 1917

The trouble may start acutely with chills and fever or usually more insidiously. The general course is that of a chronic obscure sepsis with rapidly progressive emaciation and great weakness and prostration. The temperature curve is irregular. The fever is never high and more or less intermittent. Many observers have noticed that there are definite periods of exacerbation and remission. There is often much sweating, especially during the periods of exacerbation. The pulse rate is usually high, often quite out of proportion to the temperature. Leukocytosis is nearly always well marked and often continued and excessive. In view of the presence of so many eosinophils in the lesions, it is curious that eosinophilia has been noted a few times only—51 per cent in one of Lamb's two cases and 30 per cent in Lewis'<sup>8</sup> case, to a less extent in the case of Pickert-Menke.<sup>9</sup> The only other more or less constant symptom is an often severe and always very annoying intermittent pain in the abdomen. This pain has not been fully explained, because it may occur even in cases in which the abdominal arteries are only slightly involved or not at all. It may be due to peritoneal irritation. The disease in most cases progresses more or less rapidly to a fatal termination lasting from a few weeks to several months, sometimes a year or more. Recoveries have been observed in a few cases, usually after intensive antisyphilitic treatment, but they also seem to occur spontaneously, and it is suspected by some that lighter cases of the disease are not so infrequent and heal without producing any severe clinical symptoms.

Other symptoms which may arise depend very much on the localization of the disease in the arteries of various organs.

The branches of the coronary arteries are most commonly involved. In them we find the typical nodules and frequently many small aneurysms. Thromboses are also common, which may cause anemic necroses in the heart muscle. Often the disease of the coronaries is associated with a more or less extensive myocarditis. In view of these severe changes in the arteries and the musculature of the heart, it is astonishing that primary cardiac weakness is observed comparatively rarely. It was well marked, however, in our own case and in that of Hart's.<sup>10</sup>

The next organ in frequency of involvement is probably the kidney. Here the lesions are often severe. The nodules in the wall of the arteries are well marked, the aneurysms numerous and the frequent thrombotic obstruction of them causes the formation of many anemic

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<sup>8</sup> Lewis. Report of a Case of Periarteritis nodosa, *Proc Path Soc Philadelphia*, n s **14** 134, 1911.

<sup>9</sup> Pickert-Menke. Ueber einen Fall von Periarteritis nodosa, *Frankfurt Ztschr f Path* **23** 313, 1920.

<sup>10</sup> Hart. Footnote 1.

esting in this connection is the case of Frankel-Wohlwill<sup>19</sup> In this patient, the arteries in the kidneys and in the stomach were badly diseased There was also a marked peripheral neuritis, but Wohlwill reports that the arteries in the affected nerves were not diseased He concludes that the lesions in the nerves were evidently due to some general toxic condition associated with the disease

While the peripheral nerves are so frequently diseased, the central nervous system usually escapes entirely Only four cases are on record in which the cerebral arteries were involved In two of these<sup>20,21</sup> multiple aneurysms had developed, one of which had ruptured, in another<sup>22</sup> the disease was limited to the small vessels of the pia, and multiple small hemorrhages were found in the brain substance<sup>23</sup> and in the last one<sup>24</sup> there was present a large area of softening due to thrombosis of a diseased artery

The nodules which sometimes occur in the small arteries of the skin have already been mentioned also the important rôle which they play in the clinical diagnosis of the disease<sup>25</sup> The little aneurysm which may form in them may rupture and give rise to the production of hematomata<sup>26</sup> In connection with the skin, attention should be called to the fact that in quite a number of cases various eruptions have been described, such as multiple erythematous spots with and without hemorrhages, purpura rheumatica, crops of urticaria and in one instance a typical erythema nodosum<sup>14</sup>

Aneurysms also sometimes form along the course of the superficial palpable arteries They have been observed in connection with the temporal and brachial arteries

19 Frankel Periarteritis nodosa Munchen med Wchnschr **64** 1538, 1917, and Wohlwill Periarteritis nodosa, Berl klin Wchnschr **55** 94, 1918

20 Chvostek and Weichselbaum Herdweise syphilitische Endarteritis mit multipler Aneurysmenbildung, Allg Wien med Ztschr **22** 257, 265, 275 294, 312, 1877

21 Dickson Polyarteritis acuta nodosa and periarteritis nodosa, J Path & Bacteriol **12** 31, 1908

22 Muller Ueber Periarteritis nodosa, Festschr d städt Krankenh Dresden-Friedrichstadt, Dresden, 1899, p 458

23 This case is also interesting because Muller in it discovered typical lesions in the retinal arteries A more careful investigation of the eyes in future cases would seem to be indicated

24 Longcope Periarteritis nodosa, with Report of a Case with Autopsy, Bull Ayer Clin Lab Penn Hosp **5** 1, 1908

25 Kussmaul and Maier Ueber eine bisher nicht beschriebene eigentümliche Arterienerkrankung (Periarteritis nodosa), Deutsch Arch f klin Med **1** 484, 1866 Muller Festschr d städt Krankenh Dresden-Friedrichstadt 1899 p 458 Freund Deutsch Arch f klin Med **62** 537, 1899 Schmorl Diskussion über Bendas Vortrag über "Aneurysma und Syphilis," Verh d Deutsch path Ges **6** 203, 1903 Von Haun Virchows Arch f path Anat **227** 90, 1920

26 Benedict Ueber Periarteritis nodosa, Ztschr f klin Med **64** 405, 1907.

The smaller branches of the gastric and mesenteric arteries are also frequently diseased, showing nodules and aneurysmal dilatation. The disease often extends down into the smallest branches in the submucosa of both stomach and intestines. If there is much obstruction in these smallest arteries hemorrhagic necroses and ulcerations occur in the mucous membrane. These ulcerations in the intestines may become so deep that they cause acute perforation and death from acute general peritonitis<sup>15</sup>. The lesions may be practically limited to the gastrointestinal tract<sup>16</sup>. Clinically the presence of such lesions might be suspected from the appearance of blood in the stools and from the occurrences of severe diarrhea, which was a prominent symptom in some instances.

Pains in the muscles of the extremities are common and are usually due to an extensive affection of the small branches of the arteries of the muscles with the development of many nodules and numerous small aneurysms. An especially interesting clinical picture may arise when the small arteries of the peripheral nerves are badly diseased. This may be followed by a widespread degeneration of the nerves and the symptoms of a severe progressive peripheral neuritis<sup>17</sup>. Here again in some cases the disease may be practically limited to the peripheral nerves and the musculature<sup>18</sup>. Whether these two cases are really cases of periarteritis acuta nodosa is a little doubtful. Most inter-

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15 Zimmermann Ueber zwei Falle von nekrosirender Enteritis bei Morbus maculosus Werlhofii, Wagners Arch f Heilk **15** 167, 1874. Lorenz Beitrag zur Kenntnis der multiplen degenerativen Neuritis, Ztschr f klin Med **18** 493, 1891. Verse Ueber Periarteritis nodosa, Munchen med Wchnschr **38** 1809, 1905. Periarteritis nodosa und arteritis syphilitica cerebialis, Ziegler's Beitr **40** 409, 1907. Beitzke Präparate eines Falles von Periarteritis nodosa, Berl klin Wchnschr **65** 1381, 1908. Ueber einen Fall von Periarteritis nodosa, Virchows Arch f path Anat **199** 214, 1910. Meyer, S Zur klinischen Erkenntnis der Periarteritis nodosa und ihre pathologisch-anatomischen Grundlagen, Berl klin Wchnschr **58** 473, 1921.

16 Veszpremi Ueber die Periarteritis nodosa, Ziegler's Beitr **52** 476, 1912.

17 Kussmaul and Maier Ueber eine bisher nicht beschriebene eigentümliche Arterienerkrankung (Periarteritis nodosa), Deutsch Arch f klin Med **1** 484, 1866. Meyer, P Ueber Periarteritis nodosa oder multiple Aneurysmen der mittleren und kleineren Arterien, Virchows Arch f path Anat **74** 277, 1878. Rosenblath Ein seltener Fall von Erkrankung der kleinen Arterien der Muskeln und Nerven, die klinisch als Dermatomyositis imponierte, Ztschr f klin Med **33** 547, 1897. Freund Zur Kenntnis der Periarteritis nodosa, Deutsch Arch f klin Med **62** 537, 1899. Lorenz Beitrag zur Kenntnis der multiplen degenerativen Neuritis, Ztschr f klin Med **18** 493, 1891. Schmincke Ueber Neuritis bei Periarteritis nodosa, Verh d Deutsch path Ges **18** 287, 1921. Meyer, S Zur klinischen Erkenntnis der Periarteritis nodosa und ihre pathologisch-anatomischen Grundlagen, Berl klin Wchnschr **58** 473, 1921. Gerlach Ueber Periarteritis nodosa, Klin Wchnschr **1** 467, 1922.

18 Damsch and Seitzke Ueber einen Fall von akuter Erkrankung der gesamten Korpermuskulatur der Kleinen Muskel und Nervenarterien, Festschrift für Orth, 1903. Joffroy and Achard Nervite périphérique d'origine vasculaire, Arch de med Exper **1** 229, 1889.

The histologic lesions are of a distinctly inflammatory character, although the destructive lesions in the media may prevail to such an extent that the signs of inflammation may be overlooked, especially with the more imperfect histologic methods in use at the time when some of the first cases were examined by Rokitansky<sup>32</sup> and Eppinger<sup>33</sup>. Rokitansky suggested that the multiple aneurysms might be due to multiple tears in the musculo-elastic coat, and Eppinger attempted to explain this by assuming the presence of a congenital weakness of the wall of the diseased arteries. Practically all later authors agree on the inflammatory nature of the disturbance. One of the most characteristic features of it in the early cases is a tremendous infiltration of the adventitia with partly neutrophilic, partly eosinophilic polymorphonuclear leukocytes mixed with a smaller or larger proportion of small lymphocytes and plasma cells. Degenerative lesions in the media tending to the destruction of muscle and elastic tissue in some cases are early and severe, so that the arteries may actually rupture, and hematomas or false aneurysms may develop. Usually the degenerative changes in the media are more moderate and of slower development, beginning with a peculiar vacuolization of the musculature and ending in a more or less rapidly progressive destruction of the elastic fibers. The diseased muscle is invaded early by the leukocytes, and these may soon find their way into the intima. The behavior of this coat varies considerably. In some cases it remains practically unaltered, in others, it shows a marked collection of fluid underneath the endothelium, which, when hardened, coagulates into a hyaline substance in which there may be masses of fibrin. Soon proliferative changes also become noticeable. These begin in the inner layer of the adventitia close to the muscle. Large masses of cells resembling epithelioid cells are found in this region. These promptly begin to invade the diseased musculature. Among these cells one also finds new capillary blood vessels, and it is these cells that show the tendency to arrange themselves in small cellular nodules which are often situated partly in the adventitia, partly in the destroyed muscle. The nodules are rich in small capillaries. They do not show any tendency to central degeneration or to caseation. Giant cells have not been found in them, although foreign body giant cells have been seen in one case in the media, which was the seat of a rapid disintegration. This new cellular tissue may run on into the intima or there may be a separate proliferation of the intimal cells as in our case, with later production of fibrous tissue in both places. Whether aneurysms form

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32 Rokitansky Ueber einige der wichtigsten Krankheiten der Arterien, Denkschr d K Akad d Wissensch Wien 4 1, 1852

33 Eppinger Pathogenese, Histogenese und Aetiologie der Aneurysmen Das congenitale Aneurysma, Arch f klin Chir 35 Suppl 42, 1887



As stated above, lesions in the bronchial arteries have been noted occasionally, but a diffuse infiltration of the bronchial mucous membrane with asthmatic symptoms seems to be one of the unique features in our case.

It is also difficult to understand why in most cases the pulmonary vessels should be entirely exempt and in Monckeberg's<sup>7</sup> and my cases so badly diseased with marked extension of the subacute inflammation into the adjoining pulmonary tissue.

The liability of the serous membranes to participate in the process has not been sufficiently recognized. This was quite a marked feature in our case and the presence of a true exudate in the pleural cavities was quite a puzzle to the clinicians. The occurrence of subacute pericarditis, pleurisy or peritonitis or several of these conditions in various combinations has been described in many cases, but no special attention has been paid to it and too little emphasis has been placed on the appearance of rather characteristic, just visible, grayish nodules in these lesions.

In conclusion, it may be stated that minor lesions have been observed in the arteries of several other organs, sometimes with more or less involvement of the parenchyma, as, for instance, of those in the pancreas or the suprarenals.

It may be readily imagined what a bewildering variety of symptoms may arise when not one, but several systems are simultaneously involved, as is usually the case. It is to be feared, therefore, that in spite of our better knowledge of the disease successful clinical diagnosis will remain a rare exception. The fact that clinicians see it so rarely will naturally contribute to this result, there are several, however, who have observed more than one case (Kussmaul,<sup>27</sup> Muller,<sup>28</sup> Lamb,<sup>3</sup> Klotz,<sup>14</sup> Vespremi<sup>28</sup>). Several cases have been seen at Fischer's laboratory in Frankfurt, five or more under Marchand at the Pathological Institute at Leipzig (Ferrari,<sup>29</sup> Verse<sup>30</sup>), three in Philadelphia (Longcope,<sup>24</sup> Cooke,<sup>31</sup> and Lewis<sup>8</sup>). This would seem to indicate that the disease is not so excessively rare as was believed at one time.

27 Kussmaul and Maier. *Deutschr Arch f klin Med* **1** 484, 1866.

28 Vespremi and Jansco. *Zieglers Beitr* **34** 1, 1903. Vespremi, *Ibid* **52** 476, 1912.

29 Ferrari. *Ueber Periarteritis nodosa und ihre Beziehungen zur Poly-myositis und Polyneuritis acuta*, *Zieglers Beitr* **34** 350, 1903.

30 Verse. *Ueber Periarteritis nodosa*, *Munchen med Wchnschr* **38** 1809, 1905. *Periarteritis nodosa und arteritis syphilitica cerebialis*, *Zieglers Beitr* **40** 409, 1907. *Diskussion zum Vortrag Jagers uber vergleichend path Untersuchungen uber Periarteritis nodosa*, *Verh d deutsch path Ges* **13** 213, 1909. *Ueber totale Pfortader-obliteration und anamische Infarkte der Leber*, *ibid*, p 314. *Periarteritis nodosa*, *Munchen med Wchnschr* **64** 1468, 1917.

31 Cooke. *A Case of Periarteritis nodosa*, *Proc Path Soc Philadelphia*, n s **14** 96, 1911.

for in sections, but with a uniformly negative result. The fact also that a disease identical with periarteritis nodosa occurs in various animals seems to make it impossible to accept syphilis as an etiologic factor. Some believe that it may act as a predisposing factor, but even this appears doubtful.

If we exclude syphilis, as I think we are justified in doing, there remain two other possibilities which have been widely discussed: (1) The disease is a special infection, "sui generis," or (2) the lesions are the result of the action on perhaps predisposed arteries of various infectious or toxic agents, the latter having been suggested on account of the general inability to demonstrate bacteria in the sections.

The idea of a special infection derives its main support from these facts: (1) A disease practically identical with it has been observed by Lupke<sup>35</sup> in epidemic form in a herd of stags, (2) twice (v. Haun<sup>36</sup> and Harris and Friedrichs<sup>37</sup>) the claim has been made that there has been a successful experimental transmission of the disease to laboratory animals. The experiments reported by von Haun are hardly convincing. He inoculated guinea-pigs intraperitoneally with blood obtained from a patient suffering from periarteritis nodosa and again inoculated other guinea-pigs from these when they were sacrificed two months later. No gross lesions were seen in any of the inoculated animals. Microscopic examination revealed suspicious lesions about some of the smaller organ arteries, but von Haun states that these vascular lesions were not pronounced, and he doubts whether the guinea-pig is a suitable animal for such experiments. Lamb<sup>3</sup> had inoculated guinea-pigs before von Haun, but with negative results, and Carling and Hicks<sup>38</sup> recently repeated von Haun's experiments in exactly the same way. They even permitted some guinea-pigs to live longer than two months, but could not detect any characteristic lesions in them either grossly or microscopically.

The experiments of Harris and Friedrichs were performed on rabbits, in a more elaborate manner. They injected emulsions from

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35 Lupke. Ueber Periarteritis nodosa bei Axishirschen, *Verh. der deutsch. path. Ges.* **10** 149, 1906. A histologic study of the lesions is given by Jaeger. *Die Periarteritis nodosa*, *Virchows Arch. f. path. Anat.* **197** 71, 1909. The disease has also been found in other animals: in cattle, by Guldner. *Virchows Arch. f. path. Anat.* **219** 366, 1915; and in hogs by Joest. *Ziegler's Beitr.* **69** 85, 1921.

36 Von Haun. *Pathohistologische und experimentelle Untersuchungen über Periarteritis nodosa*, *Virchows Arch. f. path. Anat.* **227** 90, 1920.

37 Harris and Friedrichs. The Experimental Production of Periarteritis nodosa in the Rabbit, with a Consideration of the Specific Causal Excitant, *J. Exper. M.* **36** 219, 1922.

38 Carling and Hicks. A Case of Periarteritis nodosa Accidentally Recognized During Life, *The Lancet* **1** 1001, 1923.

depends first, on the extent of destruction in the musculature, and secondly, on the amount and resistance of the new fibrous tissue. If the latter is voluminous, the lumen of the vessels is likely to be more or less completely obstructed. Since the disease is usually focal, these masses of fibrous tissue in the wall of the small arteries produce a more coarsely nodular appearance. The still larger nodules, from the size of the kernel of a cherry or larger, are usually aneurysms, which may become solidified by the organization of thrombus in them. These multiple small aneurysms are the most striking phenomenon in many of the older cases. They are not essential and are purely secondary developments.

A discussion of the exact seat of the primary lesions in the wall of the affected arteries, I believe, is futile, because soon all three coats become involved in the process.

#### ETIOLOGY OF PERIARTERITIS NODOSA

The question of the etiology of the condition is of much greater importance. In regard to this, three theories have been advanced and are being supported by more or less convincing arguments by the various writers.

At the suggestion of Virchow, who had seen some of the sections of Kussmaul's case, Kussmaul tentatively mentioned the possibility of a syphilitic origin, and since then this idea has found several advocates, most prominent among them being Versé, who has seen more cases of this disease than any one else. In one of his papers published in Ziegler's *Beitrag* in 1907, he makes a careful comparison between the findings in his case<sup>34</sup> and several specimens of true syphilitic arteritis, and he arrives at the conclusion that the lesions in the two diseases are quite similar. He is therefore inclined to believe that the disease may be a modified form of syphilis. The existence of a certain similarity, especially in the older lesions of the two diseases, is undeniable but the incipient stages are quite different, the heavy infiltration with granular leukocytes does not occur in syphilis, the granulomas which form later do not caseate, the accumulation of a serofibinous exudate also points to a much more active inflammatory process than that which is caused by *Spirochaeta pallida*. The comparative rarity of a syphilitic history in patients suffering from periarteritis and the almost constant absence of a Wassermann reaction also speak against a connection of the lesions with a syphilitic infection. If the lesions were truly syphilitic, they would be of an exceptionally acute nature and therefore should contain the infectious agent in large numbers. In sixteen cases of periarteritis nodosa spirochetes have been searched

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34 Verse    Ziegler's Beitr 40 409, 1907

Klotz'<sup>11</sup> case showed a typical erythema nodosum. In one of the most acute cases of the whole series,<sup>2</sup> the disease developed immediately following an injury to the hand, with consecutive abscess formation in the soft parts of the upper arm. Unfortunately there is no record of a bacteriologic examination of the abscess, but the opening of it was followed by an erysipelatous condition of the adjoining skin. During the course of the disease an erythema appeared on the skin elsewhere, which wandered from one place to another and in the end also showed a great resemblance to erysipelas. The patient in Schrieber's case<sup>43</sup> was suffering from chronic nonsyphilitic ulcers of the skin of the legs when the disease developed, and the patient in Lewis'<sup>8</sup> had an infected lacerated wound of the scalp. Kroetz' patient<sup>44</sup> had a septic infection of the urinary tract. Endocarditis was present in five cases<sup>45</sup>. It was mostly acute, in some cases more chronic. In Lamb's, diplostreptococci were found on the diseased heart valves and in other parts of the body.

In the discussion of Lupke's paper before the German Pathologic Society, Aschoff pointed out that apart from the possibility of a syphilitic origin in periarteritis nodosa, a rheumatic infection also should be considered in view of the similarity of the "rheumatic" nodules to the small granulomatous nodules in periarteritis. The rheumatic nodules, although usually confined to the adventitia, might destroy the media deeply. (A characteristic case of this kind is given by Geipel. Myocarditis, *Munchen med Wchnschr* 54 1057, 1907.)

If it is true that certain forms of nephritis are caused by infections of this character, the frequent coincidence of periarteritis nodosa and acute and subacute glomerulonephritis is highly suggestive<sup>46</sup>. In this connection, it is interesting to recall that in early glomerulonephritis eosinophils are commonly found in the lesions.

So far as the actual finding of streptococci is concerned, their presence has never been demonstrated in the lesions in spite of the

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43 Schrieber. Ueber Periarteritis nodosa, Inaug. Diss. Königsberg, 1904.

44 Kroetz. *Deutsch Arch f klin Med* **135** 311, 1921.

45 Muller. *Festschr d städt Krankenh Dresden-Friedrichstadt, Dresden*, 1899, p 458. Benda. Ueber die sog Periarteritis nodosa, *Berl klin Wchnschr* **45** 353, 1908. Lewis. Report of a Case of Periarteritis nodosa, *Proc Path Soc Philadelphia*, n s **14** 134, 1911. Lamb. *Arch Int Med* **14** 481, 1914. Lowenberg. Beitrag zur Klinik der Periarteritis nodosa, *Med Klin* **19** 207, 1923.

46 Graf. Ueber einen Fall von Periarteritis nodosa mit multipler Aneurysmenbildung, *Zieglers Beitr* **19** 181, 1896. Rosenblath. *Ztschr f klin Med* **33** 547, 1897. Freund. *Deutsch Arch f klin Med* **62** 537, 1899. Dickson. Polyarteritis acuta nodosa and periarteritis nodosa, *J Path & Bacteriol* **12** 31, 1908. Oberndorfer. *Munchen med Wchnschr* **54** 2618, 1907. Bomhard. *Virchows Arch f path Anat* **192** 305, 1908. Longcope. *Bull Ayer Clin Lab Penn Hosp* **5** 1, 1908. Veszpremi. *Zieglers Beitr* **52** 476, 1912. Lamb. *Arch Int Med* **14** 481, 1914. Klotz. *J Med Res* **37** 1, 1917.

the diseased tissues intravenously into two rabbits, and from these they inoculated others with filtered and unfiltered tissue emulsions. The animals lived from two to six and one-half months. None of them showed gross lesions except rabbit C, which died after one month. This animal showed some rather coarse nodules in the lungs, which may have been due to embolism. The authors give photomicrographs of the lesions, among which Figures 8 and 11 are suggestive of a positive result. I believe, however, that even these experiments are not entirely convincing. Lamb also reports negative inoculation experiments in rabbits, and our own experiments with the same animal have been negative. It must be stated, however, that the first inoculations by us were made about thirty-six hours after necropsy and not intravenously but intraperitoneally.

Whatever the final result of this experimental work may be, it is of value to look at the question from one more point of view and to study the apparently close relation which exists between periarteritis nodosa and the ill-defined group of subacute and chronic "septic" conditions with so-called "rheumatic" symptoms and frequently associated with endocarditis. Of the close pathologic relationship of these "rheumatic" processes there is no doubt, but whether they form an etiologic entity also by being caused by various types of streptococci is not quite so certain. There are some, however, who still believe that rheumatic fever is caused by some as yet unknown special infectious agent. One need not study many cases of periarteritis to discover its close relation to this group. This has been commented on by many authors. The evidence connecting the two conditions is of all kinds—clinical, pathologic and bacteriologic. In several cases,<sup>39</sup> there is a definite history of a recent attack of rheumatism, in others, the disease was ushered in by an acute attack of tonsillitis,<sup>40</sup> in one case with abscess formation.<sup>41</sup> During the course of the illness almost all clinicians have been impressed with the resemblance of the syndrome to that of a slow, comparatively mild septic condition, and various skin eruptions have been observed which seemed to favor this impression. These were either erythematous or resembled purpura rheumatica.<sup>42</sup> In one case,<sup>28</sup> the efflorescences were more of an urticarial nature and

39 Rosenblath *Ztschr f klin Med* **33** 547, 1897. Muller *Festschr d stadt Krankenh Dresden-Friedrichstadt, Dresden, 1899*, p 458.

40 Oberndorfer *Munchen med Wchnschr* **54** 2618, 1907 and Bombard *Virchows Arch f path Anat* **192** 305, 1908. Hart *Berl klin Wchnschr* **45** 1305, 1908, and Kunne *Frankfurt Ztschr f Path* **5** 105 1910. Lamb *Arch Int Med* **14** 481 1914. Klotz *J Med Res* **37** 1, 1917. Mertens *Klin Wchnschr* **1** 1844 1922.

41 Walter *Beitrag zur Histopathogenese der Periarteritis nodosa, Frankfurt Ztschr f Path* **25** 306, 1921.

42 Zimmermann *Wagners Arch f Heilk* **15** 167, 1874. Schreiber *Inaug Diss Konigsberg, 1904*. Lamb *Arch Int Med* **14** 481, 1914.

usually more focal in character and associated with more cicatrization in media and adventitia than that which we ordinarily find in simple arteriosclerosis. Any one who has studied an extensive pathologic material must recall cases of especially severe arteriosclerosis of the peripheral arteries with much scarring, with a marked tendency to dilatation and even to the development of aneurysms. There are transitions from such cases to the more common type of arteriosclerosis in which the lesions are more strictly confined to the intima. Personally, I should feel inclined to group all these changes together as arterial inflammations, particularly as I am becoming convinced more and more that primarily arteriosclerosis is due to a true inflammation of the arterial wall, only modified later on by degenerative and reparative processes. This would, of course, not mean that we should postulate an acute inflammatory beginning like that observed in cases of periarteritis for all cases of chronic arteriosclerosis. The severe forms which I have alluded to actually may have a more acute beginning than we are now inclined to believe. In fact, our general experience in this regard makes it quite probable that we have been unduly skeptical in trying to visualize the early stages of this and other chronic inflammatory conditions. When we do see these early lesions we are usually amazed at the tremendous involvement of the tissues. I believe, however, that it is equally clear that even the earliest lesions in ordinary arteriosclerosis are mild in character when compared with those in periarteritis, but this should not prevent us from trying to apply the lessons taught by the more acute disease to the more chronic conditions. In this way we might obtain some clues in regard to the etiologic possibilities of the more obscure chronic conditions, we might also understand better their histogenesis and that of the lesions in the various organs which are so commonly associated with them.

#### CONCLUSIONS

1 Periarteritis nodosa is an acute inflammatory disease of the smaller arteries, usually focal in character, which may involve any and all vascular territories.

2 It probably starts in the adventitia, but soon involves all coats of the arterial wall and leads to the development of microscopic granulomatous nodules, later to coarser fibrous nodules in the wall of the affected arteries, and eventually to the formation of multiple aneurysms. Thrombosis is common in the diseased arteries and may lead to necroses in the tissues (infarcts, hemorrhagic necroses and ulcers).

3 The inflammation may extend from the arteries into the adjoining tissues. The serous and mucous membranes are likely to become involved in the process.

fact that sections have been carefully examined bacteriologically in about one half of the cases Bomhard<sup>12</sup> reports finding few cocci in the peripheral zone of the lumen of a blood vessel, and Longcope<sup>24</sup> observed a few cocci in sections of the kidney Blood cultures during life which were made in ten cases, sometimes repeatedly, uniformly remained sterile with the one exception of one flask in our case which contained streptococci Beitzke<sup>47</sup> isolated streptococci from the heart blood at necropsy In our case, a guinea-pig which was inoculated intraperitoneally with an emulsion of diseased tissue died of acute streptococcic peritonitis I have already mentioned that in Lamb's<sup>3</sup> case a typical diplostreptococcus endocarditis was present Beattie and Douglas<sup>48</sup> obtained a pure culture of streptococci from the subcapsular hemorrhage in the right kidney Jonas<sup>49</sup> found streptococci in a culture from the kidney Lamb's<sup>3</sup> careful cultural work was entirely negative, except for his recovering streptococci in a tissue culture from one of the aneurysms of the heart The whole question of the relation of streptococcus infection to the disease has been most carefully studied by Klotz In both of his cases<sup>14</sup> he recovered streptococci, in the first one from the gallbladder (*Streptococcus mitis*) and in the second one from the heart blood, bile, subcapsular lymph channels of the liver (*Streptococcus anginosus* or *Streptococcus salivarius*) He also attempted to reproduce the characteristic lesions of the disease by inoculating the streptococci obtained from his cases about the celiac axis and into the anterior mediastinum of rabbits *Streptococcus anginosus* proved too virulent, killing the animals in twenty-four hours, but with the less virulent cultures at times a subacute periarteritis with slight involvement of the media was obtained On the whole, there is not much direct evidence of the importance of the streptococcus in periarteritis nodosa, but this is true also of other manifestations of this group of rheumatic conditions, the connecting link between which is not plainly apparent at the present time It is possible that in such rheumatic conditions the streptococcus may play only the rôle of a frequent secondary invader

Do these observations on periarteritis acuta nodosa add anything to our understanding of the more chronic diseases of the arteries in particular to our knowledge of arteriosclerosis? In the chronic cases of periarteritis marked scarring of the walls of the affected arteries eventually develops, and a condition arises not dissimilar to severe arteriosclerosis of the peripheral arteries, although the lesions are

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47 Beitzke Berl klin Wchnschr **65** 1381, 1908 Virchows Arch f path Anat **199** 214 1910

48 Beattie and Douglas A Case of Periarteritis Nodosa, J Path & Bacteriol **17** 194, 1912-1913

49 Jonas Periarteritis Nodosa, Munchen med Wchnschr **59** 1685, 1912

# THE BACTERIOPHAGE IN THE TREATMENT OF INFECTIONS \*

EARL B. MCKINLEY, M.D.

DALLAS, TEXAS

It is premature to draw elaborate conclusions regarding the efficacy of the bacteriophage in the treatment of infections. However, we feel that our success in a number of cases is of sufficient importance to present these cases at this time.

The bacteriophage was found by d'Herelle<sup>1</sup> in 1917 in the stools of patients convalescing from dysentery. The filtrates from broth cultures of these stools exhibited an interesting phenomenon. When added in amounts varying from 2 drops to 2 cc. to young broth cultures of Shiga dysentery, it was found that these bacterial suspensions became limpid after a few hours in the incubator and were as clear as water. When again slant subcultures were made from these tubes, after several hours' incubation one noted either a sterile slant (a pure culture of the bacteriophage) or multiple minute round clear areas in which no bacteria grew, and these d'Herelle has called "colonies" of bacteriophages. Touching one of these clear areas with a sterile platinum loop, this "lytic substance" could be transplanted to other young broth suspensions of Shiga dysentery bacilli, and the phenomenon would again be repeated.

Here, then, is a "substance" isolated from the intestinal tract of man which possesses the property of actually dissolving bacteria and which grows or increases at the expense of bacteria. It cannot be described accurately as bactericidal or germicidal, but it is lytic in that the organisms are completely destroyed without fragments remaining. In 1915, Twort<sup>2</sup> observed a similar phenomenon, perhaps the same, though there is still controversy regarding this. It is possible, however, that Hankin<sup>3</sup> in 1896 first observed the phenomenon in the waters of certain rivers in India when working with the cholera vibrio, though we cannot be sure of this.

In brief, the bacteriophage is a "lytic substance" which has the property of dissolving bacteria. D'Herelle believes it to be a living organism which parasitizes bacteria, although others have thought it to be enzymatic in nature.

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\* From the Department of Bacteriology and Preventive Medicine, Baylor University College of Medicine.

1. D'Herelle, F. *The Bacteriophage*, English edition, March, 1922.

2. Twort, F. W. *An Investigation on the Nature of Ultra-Microscopic Viruses*, *Lancet*, 2: 1241, 1915. *Researches on Dysentery*, *Brit. J. Exper. Path.* 1: 237, 1920.

3. Hankin, E. H. *L'Action bactericide des eaux de la Jumna et du Gange*, *Lancet* 10: 511-523, 1896.



4 The etiology of the disease remains obscure, but the observations suggest some relation to subacute "septic rheumatic" infections

5 The clinical picture of the disease is that of a subacute infection with local symptoms resulting from the more or less marked involvement of various organs

#### ABSTRACT OF DISCUSSION

DR H E ROBERTSON, Rochester, Minn I believe that periarteritis nodosa is much more common than is ordinarily supposed It is probably true that virtually every granulomatus infection in the body gives rise to periarteritis nodosa to a certain extent We do not term it that because the involvement of the arteries is often not the chief feature of the disease In this particular disease it would seem that we were dealing not so much with a special cause as with a tissue specificity Perhaps that is a distinct disease, but the chances are probable that we are dealing with a form of rheumatic disease in which we have a tissue specificity, and this is true practically of every type of rheumatism with which we have to deal If we could only determine its specificity—its pathogenicity we call it, but it is really its specificity—we could probably get a stage in a particular subject or particular animal at which any organism might produce this sort of picture

DR WILLIAM OPHULS, San Francisco Aschoff himself has suggested the great similarity, at times, of these granulatomas in periarteritis and his rheumatic nodules A case in point has been published by Geipel So far as the frequency of the disease is concerned, I may say this that as the disease has become better known it has apparently become more frequent There are also some investigators who have seen several cases For instance, Verse in Germany has mentioned in literature four or five cases and probably has seen more, in our own country there were three observed in Philadelphia within a comparatively short time So the disease is one that, when carefully searched for microscopically, is comparatively frequently found It may very well be overlooked if microscopic sections are not made Predisposition certainly plays a marked role in it It is only special types of individuals who develop periarteritis nodosa

cases of true typhoid fever and two cases of paratyphoid B infection treated with the bacteriophage. Three of these patients received the treatment by simultaneous injection and ingestion, and the others by ingestion alone. They state that within forty-eight hours defervescence with euphoria occurred, and the apyrexia remained permanent. Two cases of typhoid fever in adults of the ataxo-dynamic form were also reported by these authors. Both of these patients were said to have pronounced myocardial involvement. The apyrexia followed the treatment within forty-eight hours, but both cases terminated fatally. The authors suggested that in these cases failure was probably due to a too long delayed intervention or to too small a dose in view of the severity of the infection. The usual amount given by mouth was 2 c c and 1 c c by injection subcutaneously. These authors describe a sudoral crisis which followed the administration in about two hours. Two cases of puerperal pyelocystitis were also reported by them due to *B. coli*. Each patient received 1 c c of an anticoli bacteriophage culture subcutaneously, and a permanent apyrexia ensued within forty-eight hours.

Courcoux<sup>6</sup> has reported a case of pyelonephritis, the first symptom of which was observed in a young woman at the sixth month of pregnancy. The bacteriophage was given by subcutaneous injection and by the injection of 15 c c directly into the bladder. He states that there was considerable reaction for forty-eight hours, and then all symptoms subsided, the improvement amounting to a clinical cure, although *B. coli* could still be cultivated from the urine.

Davison<sup>7</sup> has reported a series of twelve cases of bacillary dysentery in children, who were treated with the bacteriophage. He concludes that the treatment did not influence the mortality or course of the disease. He suggests that failure in these cases might be due to the fact that in the majority the treatment was commenced late in the disease. The only two patients treated within the first week of the onset of the disease recovered.

Our cases represent a variety of infections. We have administered the bacteriophage by nearly every route possible except intravenously and intraspinally. We have administered the material in amounts varying from 1 c c up to 50 c c. At the outset we decided that some method should be devised of standardizing the bacteriophage so that we would have some fairly definite idea of the amount we were giving. We have obtained our bacteriophages from a variety of sources.

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<sup>6</sup> Courcoux, A. Pregnancy Pyelonephritis, Bull. et mem. Soc. méd. d. hôp. de Paris **46** 1151, 1922.

<sup>7</sup> Davison, W. C. The Bacteriolysant Therapy of Bacillary Dysentery in Children, Am. J. Dis. Child **23** 531-534, 1922.

In Part 2 of d'Herelle's book he discusses the bacteriophage in disease. He reports five cases of bacillary dysentery in patients from 6 to 70 years of age. All five cases were due to the Shiga bacillus. In the stools in each case the bacteriophage was present and active against the infecting organism. All of these patients recovered. Recovery, according to d'Herelle, was due to the presence of the bacteriophage in the intestinal tract. A sixth patient, a man, aged 56, was infected with the Hiss strain. A bacteriophage was isolated which was lytic for a stock strain of the Hiss bacillus, but only after twelve subcultures of the Hiss strain from the patient (in other words, when the organism was attenuated) did the bacteriophage become completely lytic for that organism. This case terminated fatally, and at necropsy the Hiss bacillus was isolated from the heart blood. D'Herelle believes this was a case of *B. dysenteriae* Hiss septicemia, and that death ensued because of failure of the intestinal bacteriophage to adapt itself to the Hiss strain responsible for the patient's infection. In other words, in disease there appears to be a conflict between the infecting organism and the bacteriophage, and the disease has a fatal issue when the bacteriophage exerts no protective action through lack of adaptation to the infecting organism, or when the pathogenic organism acquires a resistance to the bacteriophage, a "refractory state" so called. In a series of other infections, including pyelonephritis (*B. coli*), typhoid fever (mild and severe cases), avian typhosis (in epizootics and also where epizootics did not exist), in barbone (hemorrhagic septicemia of the buffalo) and in rats harboring *B. pestis*, d'Herelle succeeded in isolating the bacteriophage which was lytic for the infecting organism in question. All of this work is interesting from the comparative standpoint, but I shall not attempt to abstract it here since it is described in detail in the literature.

D'Herelle reported five cases of bacillary dysentery in patients from 3½ to 12 years of age, all of which were due to Shiga dysentery. In each case the only treatment instituted was the ingestion of the culture of the bacteriophage. All of these patients were having bloody stools, one as few as five to seven a day, and others so many that they could not be counted. All of these patients were cured bacteriologically and clinically and were discharged from the hospital from nine to fourteen days after admission.

Bruynoghe and Maisin<sup>4</sup> have reported the successful use of the bacteriophage by subcutaneous injections in conditions due to the staphylococcus and anthrax. Beckerich and Hauduroy<sup>5</sup> have reported five

4 Bruynoghe, R, and Maisin, J. Essais de therapeutique au moyen du bacteriophage du staphylocoque, *Compt rend Soc de biol* **85** 1120-1121, 1921.

5 Beckerich, A., and Hauduroy, P. Le bacteriophage dans le traitement de la fièvre typhoïde, *Compt rend Soc de biol* **86** 168, 1922.

aching pain at times radiating from the scrotum on the left side up to the abdomen. His best weight was 165 pounds (74.84 kg), twenty years ago. His present weight is 133 pounds (60.3 kg) and he says that he has been gradually losing weight since 1918. The Wassermann test was negative.

*Laboratory Examinations*—The gastric content showed a deficiency in hydrochloric acid. The bile and blood were normal. The urine showed no albumin, no sugar and no casts, but occult blood was present on three examinations.

*Treatment and Course*—Dr. H. L. Cecil was asked to see the patient, and a diagnosis of stone in the left kidney was made, which was confirmed by roentgen-ray examination. Dr. Cecil removed this stone on January 1. The patient made a rapid and uneventful recovery.

January 17. Examination of catheterized specimens from each kidney revealed that both kidneys were loaded with staphylococci. The right kidney was treated with silver nitrate, and 8 c.c. of a staphylococcus bacteriophage were introduced through the catheter into the pelvis of the left kidney.

January 20. Specimens showed only a few staphylococci present in the left kidney, with more in the right. Eight cubic centimeters of bacteriophage were introduced into the pelvis of the right kidney.

January 24. We were unable to catheterize the left ureter. Staphylococci still present in the right kidney. Eight cubic centimeters of bacteriophage were again introduced.

January 27. Unable to catheterize the left kidney pelvis. Few staphylococci were obtained from right kidney. Eight cubic centimeters were again introduced.

January 30. Specimens from both kidneys were negative for organisms.

February 15. Specimens were negative for staphylococci. The patient weighed 137 pounds (62.1 kg).

February 24. Voided specimen contained few cocci.

March 1. The patient's condition was the same as on last examination.

June 12. The patient was feeling well and was entirely relieved of symptoms.

In this case the results should not be emphasized too strongly. Pyelitis frequently clears up of its own accord after removal of stones, as in cases without stone. At no time was there any reaction following the administration of the bacteriophage. No sudorial crisis was observed such as other authors have described.

*CASE 2—History*—A. I. W., a laborer, aged 38, entered Dr. M. E. Lott's service on February 10. His family and past history was unimportant. On Nov. 24, 1922, the patient was building a fire escape for a school house and was pulling up the lower section of a balance trackway with a block and tackle when the timber gave way at the top of the building falling four stories, striking his left arm and knocking him from his feet.

*Treatment and Course*—He was operated on, and a piece of bone about 4 inches (10.16 cm) long was removed. The wound was badly infected and discharged profusely, having a bad odor. On February 12, he was operated on a second time at this hospital, and the wire used in the first operation was removed. The wound discharged continuously for two weeks, soaking the dressings so that it was necessary to dress the arm two or three times daily.

February 26. Two and one-half cubic centimeters of staphylococcus bacteriophage were injected into the wound and into the surrounding tissue.

February 27. During the preceding twenty-four hours there had been scarcely any discharge. The same treatment was again instituted.

February 28. The condition was much improved. There was practically no discharge. The same treatment was again given.

(McKinley<sup>8</sup>) A sample sent us by d'Herelle has been used for a control in testing our various filtrates. The standard we have adopted in measuring the strength of our material is simple. When we have tested a filtrate and found it to be positive for bacteriophages, the virulence has been increased by the technic described by d'Herelle until sterile agar slant subcultures are obtained. At this point the filtrate (usually from 30 to 50 c c) is placed in a large sterile test tube, and 1 c c of a twelve-hour broth culture of the organism (from stock) containing two billion organisms is added to the filtrate. The filtrate is incubated for twenty-four hours. If the filtrate is lytic for this number of bacteria, the process is repeated on the second day, at which time 2 c c of a twelve-hour broth culture of the organisms are added. The filtrate is again incubated for twenty-four hours. It usually remains clear, and the process is repeated on the third day with 3 c c of a fresh young broth culture of the organism for which we are building the bacteriophage. On the fourth day, 4 c c of broth culture are added, and on the fifth day, 5 c c. The result is a filtrate lytic for a total of about thirty billion bacteria in six days, for ten billion of which it had been lytic on the last day. If the filtrate remains clear, it is of course unnecessary to filter, but as a precaution we have always filtered the material and incubated the filtrate for twenty-four hours to prove its sterility before administering it to the patient. In the following cases we have used filtrates containing bacteriophages of the standardized strength I have described and adapted to the organism (McKinley<sup>9</sup>) causing the patient's infection.

#### REPORT OF CASES

CASE 1—C. F. V., a dental student, a man, aged 41, married, came to see me on Dec. 20, 1922. The family history was not important. He had had gonorrhea in 1900 and malaria in 1911, from which he was not entirely free until 1914. He had never used alcohol. He had used tobacco since he was 17. The present illness began in June, 1918, while he was in France, with diarrhea, frequency of urination and exhaustion. He passed from ten to twelve stools a day without blood, with little odor but considerable mucous. After two weeks' rest in the hospital, he was somewhat relieved. Four weeks later he noticed a dull aching pain and a tender area about the size of a quarter beneath the costal margin on the right side, especially marked following heavy work, long hikes, etc. On September 24, he fell exhausted and was taken to the hospital, where a diagnosis was made of mucous colitis, gastritis and probably appendicitis. He rested in the hospital for about a month, and then returned to the troops. He said that the frequency of urination had continued, and he now began to notice pain and smarting in the urethra. His condition remained about the same until March, 1919, when he passed about a quarter of a tea cup of creamy white, frothy material that burned and smarted exceedingly. His condition has remained the same until the present time. He now complains of a dull

8 McKinley, E. B. Further Notes on d'Herelle's Phenomenon, 1923 J Lab & Clin Med, in press.

9 McKinley, E. B. Notes on d'Herelle's Phenomenon, J Lab & Clin Med 8: 311-317, 1923.

his right forearm Three days later the swelling ruptured On March 24, he was operated on, and the bone was curetted Roentgen-ray examination showed an osteomyelitis with sequestrum formation

*Examination*—Examination on April 2 revealed a wound discharging large amounts of foul-smelling pus Two cubic centimeters of bacteriophage were given subcutaneously and 2 c.c. were injected into the lesion The infecting organism proved to be a staphylococcus

*Treatment and Course*—April 3 The lesion appeared to be much better, and there was little pus The same treatment was again instituted

April 4 The wound was much improved There was only one small spot on the dressing where before the dressings were soaked with the discharge

April 5 One cubic centimeter of bacteriophage was injected into the wound subcutaneously The wound continued to improve

April 7 The same treatment was given as on April 5 The wound was healing

April 11 The wound was healing There was no discharge Two cubic centimeters of bacteriophage were given subcutaneously

April 20 The wound was about one-third its original size There was no discharge Two cubic centimeters of bacteriophage was given on dressing

April 27 Only a narrow area was not healed There was no discharge No treatment was given

May 31 The patient returned and said that his wound had been entirely healed for nearly three weeks

In this case also the interesting point to note is the marked decrease in the amount of discharge even after the first treatment It is impossible of course to state whether or not this wound would have healed in six weeks after operation without the bacteriophage treatment I feel, however, that the treatment with bacteriophage in this case as in the preceding case was directly responsible for the immediate decrease in the amount of discharge, and thus facilitated healing

*CASE 4—History*—F. N., a postal clerk, aged 39, entered Dr. S. Webb's service on March 9 His family history was unimportant He had had the usual children's diseases He had had pneumonia ten years before and influenza in 1918 He had had no operations There was no history of venereal disease His present illness began three weeks before He was pitching mail with his right arm into various pigeonholes when he suddenly noticed a sharp pain in his right side under his arm The pain increased so that he stopped work the next day The following day he returned to work and worked two days He said that the pain was getting worse all the time, and it began to pain him when he breathed He went to bed and put a mustard plaster over his chest and side The pain became intense, especially on coughing or sneezing, and was located only on his right side and on the anterior surface of his chest He had had a mild cold for several months

*Examination*—There were several badly decayed teeth and marked pyorrhea There was a dull area on the right side of the chest extending from the axilla to near the sternum and below the third interspace A change of level was noticed in lying down and sitting up positions Vocal fremitus was decreased on the right side Laboratory examination revealed white blood cells, 17,000, polymorphonuclears 87 per cent Urinalysis was negative Fluid from the chest showed a specific gravity of 1.022, 96 per cent polymorphonuclears, 4 per cent mononuclears and a large amount of albumin There were many streptococci in the smear Roentgen-ray examination showed an abscess in the lower part of the right lung

February 29 The patient appeared much improved, and the wound was granulating well. Four cubic centimeters of bacteriophage were injected deep into the wound. The treatment was given about 10 o'clock in the morning. At noon the patient had a chill, and 1 o'clock the temperature was 101 F, and the patient was put to bed. The temperature was 104 F, by 2 o'clock, the pulse rate was 120. Blood examination revealed white blood cells, 19,000, polymorphonuclears, 94 per cent. By 4 o'clock the temperature was down to 102 F, and at 7 o'clock that night it was normal. The patient was up and around the next day, somewhat weak but otherwise as well as usual. The wound was much improved, and there was no discharge.

March 4 The wound was healing, and the patient left the hospital.

The rapid decrease in the amount of discharge following the treatment with the bacteriophage is the interesting fact to be noted. After

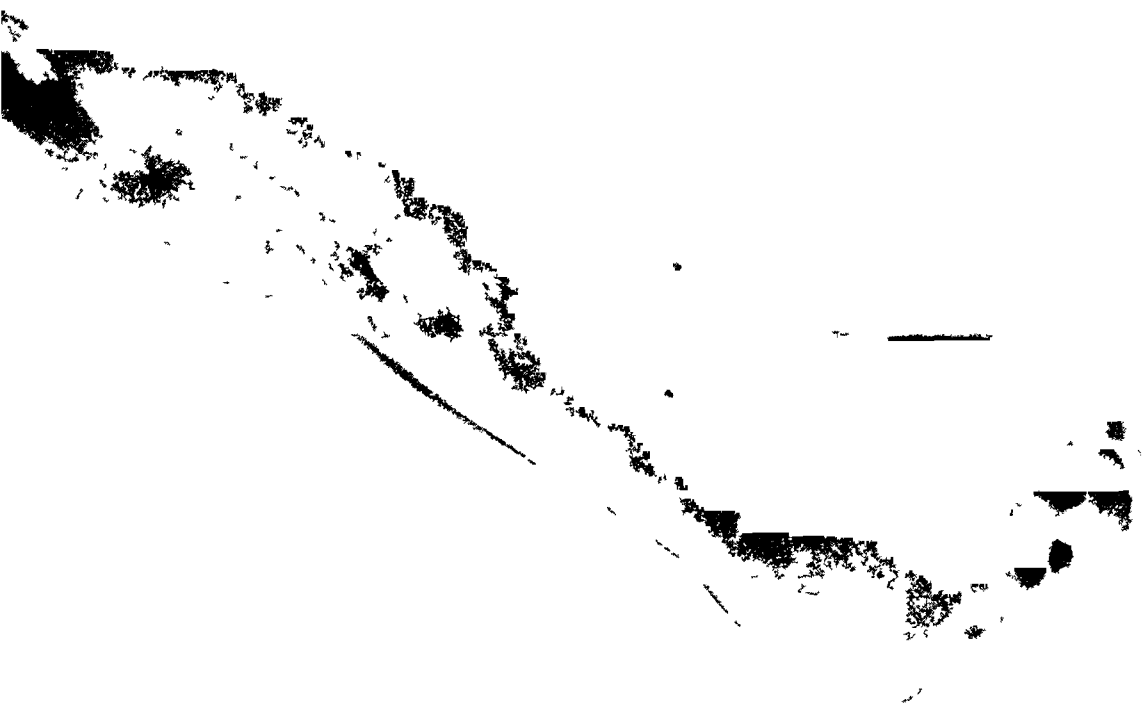


Fig 1 (Case 3) —Healed wound thirty-five days after beginning treatment with bacteriophage

almost four months of infection, the patient was highly enthusiastic with the results obtained. I do not feel that the reaction described was due to the material injected, but was due rather to the stirring up of the infection (perhaps a pus pocket) deep within the tissues. This is of course to be guarded against when injecting the material into infected wounds, although there appeared to be no resistance to the flow of the material when injected in this case.

CASE 3—*History*—L McN, a negro school boy, aged 14, entered Dr S D Weaver's service on March 20. His family and past history was unimportant. In December, he was carrying some heavy timber and noticed a swelling on

April 10 Two cubic centimeters of staphylococcus bacteriophage were injected into the discharging wound and subcutaneously around the wound

April 11 The discharge was markedly decreased

April 12 Two cubic centimeters of bacteriophage were again injected into the wound and subcutaneously around the wound One cubic centimeter was given subcutaneously into the right arm

April 13 There was practically no discharge

April 14 The wound appeared much improved There was practically no discharge

April 15 The condition was about the same

April 16 Two cubic centimeters of bacteriophage were again injected into the wound and subcutaneously around it Treatment was given at 8 o'clock in the morning At noon the temperature was 103 F The patient began to have cramping pains all over the body and marked emesis Chills were marked and lasted until 5 o'clock that afternoon

April 17 The patient's condition was a little improved The wound was healing well There was no discharge

April 18 His general condition was much better His temperature was normal He had no chills He had little nausea but felt weak The wound was healing well



Fig 3 (Case 5)—Healed wound on June 2 following treatment with the bacteriophage

April 23 The patient's condition was good The wound was healing There was no discharge The wound, formerly about 1 inch (2.54 cm) deep, continued to heal, and on May 18 healing was nearly complete, except for a slight depression which contained a small amount of blood clot

May 18 The blood clot was cleaned out, and a bacteriophage was placed on the dressing and laid over the wound The patient had a marked reaction, beginning about 8 o'clock that night, simulating the one described above, only more marked He was nauseated and had chills and fever for a week, together with marked swelling of the right leg and foot

June 2 The wound was healed Roentgen-ray examination showed union of the fractured bones

The effect on the drainage was as marked in this case as in the cases already described The reaction in this patient we are inclined to attribute to the protein in the filtrate This is largely suggested by the second reaction when the material was simply placed on the dressing and applied to the wound, which appeared to be practically healed



*Treatment and Course*—March 13 A rib resected and drainage instituted  
 March 14 There was considerable drainage with a foul odor  
 March 15 The condition was the same  
 March 17 The condition was the same Thirty cubic centimeters of a streptococcus bacteriophage were injected into the cavity  
 March 18 There was a large amount of drainage The odor was not so bad  
 March 19 There was a small amount of drainage and hardly any odor  
 March 20 Thirty cubic centimeters of bacteriophage were injected into the cavity There was little discharge and no odor  
 March 21 The condition remained the same  
 March 22 There was practically no discharge and no odor  
 March 23 There was no discharge Twenty-five cubic centimeters of bacteriophage were injected into the cavity  
 March 25 The patient was discharged from the hospital He said that he "felt fine"  
 May 15 The patient returned and said that he had felt perfectly well since leaving the hospital



Fig 2 (Case 5)—Wound on leg April 12, day of second treatment with bacteriophage

In this case also the effect of the bacteriophage on the character and the amount of the discharge is to be noted The marked odor so frequently associated with these cases had disappeared in the course of forty-eight hours following the treatment

*CASE 5—History*—J N C, a sheet metal worker, aged 57, entered Dr M E Lott's service on October 11 His family and past history was unimportant On October 11, the patient was putting up a water gutter around the roof of a two-story school building when the scaffold fell, and he fell 30 feet to the ground, landing on both feet He suffered a compound commuted fracture of the right tibia and fibula and a crushing fracture of the os calcis, with dislocation of the astragalus of his left foot

*Treatment and Course*—He was brought to the hospital, and the bones of his right leg were set and the leg put in a plaster cast The left foot was also put in a plaster cast On March 26, a piece of bone about 3 inches (7.62 cm) long was removed from his right leg, and the cast reapplied The wound was badly infected with *staphylococcus aureus*

All other medication failed to give her any relief. According to d'Herelle's theory, this recurrence was due to the organism becoming "refractory" to the bacteriophage.

**CASE 7—History**—T. T. E., a laborer, aged 23, entered Dr. M. E. Lott's service on January 28. His family and past history was unimportant. On January 28, he fell from a 43 foot (1307 cm.) derrick and broke both arms and his right leg at the junction of the upper and middle third of the femur. His leg was operated on, January 28, and bone splints were placed. The wound had been discharging large amounts of pus (*Staphylococcus aureus*) for four weeks before he entered the hospital.

**Treatment and Course**—February 24. Three cubic centimeters of staphylococcus bacteriophage were injected into the wound and surrounding tissues.

February 25. No improvement was noted.

February 26. The patient's condition was about the same. Three cubic centimeters of bacteriophage were again injected into the wound and surrounding tissues.

February 27. The discharge was markedly decreased.

February 28. Four cubic centimeters of bacteriophage were injected into the wound.

March 4. The wound was healing. One sinus opening was completely healed. There was a slight discharge of clear serum.

March 14. The wound was practically healed. There was no discharge.

While the results in this case were not so immediate or so marked as in the previous cases of similar nature which were treated, the final result, so far as the infection was concerned, was satisfactory. It will be noted that there was no reaction in this patient following the treatments with the bacteriophage.

In addition to the cases we have described above, we have treated two patients with sinus infection both giving a history of nearly four years' duration. One of these patients was operated on two years ago, when the maxillary antrum was opened. He obtained no relief. Both patients complained of a marked greenish foul-smelling nasal discharge and headache. The latter symptom was relieved in one when glasses were prescribed. The other patient obtained no relief. Both patients were given bacteriophage cultures in sterile atomizers, and were told to introduce the material in the usual manner. Both cases have run about the same course following the treatment. A day after treatment there would be a profuse discharge, and then there would be no discharge for from ten days to two weeks, and then it would begin again. After repeated and concentrated treatments, neither case has cleared up entirely although both patients have obtained the temporary relief described. Both patients were medical students. In another student giving a history of a discharging left ear since he was 4 years old following scarlet fever, we have introduced the bacteriophage in 1 c.c. amounts into the ear. The first treatment was given into the ear on May 14, although he had previously received 1 c.c. subcutaneously on

CASE 6—*History*—Miss E L C, a school teacher, aged 27, entered Dr H G Walcott's service on March 9 Her family history was unimportant The patient had had scarlet fever and whooping cough when a child, with good recovery Her appendix was removed five years before She had had influenza in February, 1922 At the end of the school year in 1922, she had had a nervous breakdown She had had a severe attack of dengue in November 1922, which lasted three weeks Her present illness began in April, 1914, with diarrhea and cramping pains in the abdomen, which had lasted until she presented herself Her stools were watery, but she had not noted any blood In April, 1922, the diarrhea became more marked, and she had had from six to ten stools a day up to the present time, and more marked during her menstrual period

Examination of the stool showed the presence of the Flexner dysentery bacillus

*Treatment and Course*—March 12 The patient was given 30 cc of bacteriophage lytic for Flexner dysentery by the duodenal tube

March 13 The patient's stool showed Flexner dysentery

March 15 The patient had only three stools

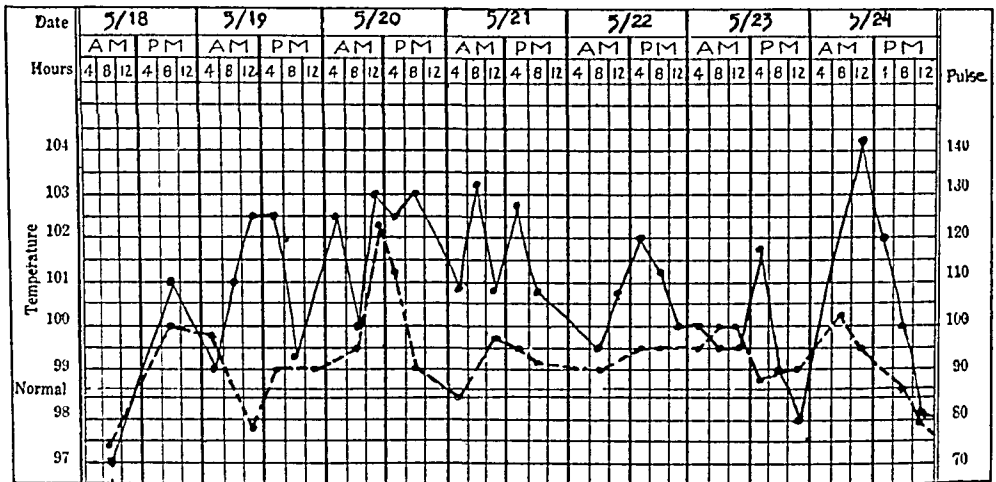


Fig 4 (Case 5) —Reaction resulting from bacteriophage placed on dressing The continuous line indicates the temperature, the broken line indicates the respiration

March 19 Thirty cubic centimeters of bacteriophage were given by the duodenal tube The patient had three stools The Flexner bacillus was not recovered from two stools

March 23 There was one formed stool The patient had just passed through the menstrual period without diarrhea The stools had been formed for the preceding four days The patient was discharged from the outpatient department, and returned home

May 30 A letter from the patient stated that she had been perfectly well but was again beginning to have diarrhea She was coming for an examination and further treatment

Treatment with the bacteriophage relieved this patient of her symptoms within a few days, and she felt perfectly well for more than two months At no time during the last nine years had she been free from diarrhea, nor had she felt as well as during the last two months

# SUBACUTE BACTERIAL ENDOCARDITIS DUE TO A HEMOLYTIC HEMOPHILIC BACILLUS

REPORT OF A CASE \*

C PHILIP MILLER, M D, AND ARNOLD BRANCH, M D

NEW YORK

In an extensive literature on the bacteriology of subacute bacterial endocarditis, there has been no mention of the hemolytic hemophilic bacilli. These organisms are closely related to the influenza bacilli, but they differ from them in one important property—their ability to hemolyze red blood cells.

These influenza-like bacilli were first described in 1919 by Pritchett and Stillman,<sup>1</sup> who recovered them from the throats of healthy persons and grouped them under the term "Bacillus X." Rivers,<sup>2</sup> in 1920, suggested that they be considered hemolytic strains of *B. influenzae*. Later in the same year, Stillman and Bourne,<sup>3</sup> defined their cultural characteristics. Walker<sup>4</sup> encountered them in his work on hemolytic streptococcus carriers. Rivers and Leuschner,<sup>5</sup> in 1921, reported on their occurrence in normal throats. They recalled that in 1918, at Fort Sam Houston, members of the Pneumonia Commission had noted hemolytic colonies of gram-negative bacilli in throats of patients with measles. Bloomfield,<sup>6</sup> in 1921, also noted their occurrence in normal persons and in patients with "common colds," in whom, however, he did not regard them as of etiologic significance. In a recent monograph on the hemoglobinophilic bacteria, in which he admirably reviews all the previous work, Kristensen<sup>7</sup> states that he has frequently encountered these bacteria, but only in healthy persons. In his summary, he tabulates the characteristics distinguishing the hemolytic hemoglobinophilic bacilli from Pfeiffer's bacilli: (a) They cause hemolysis. (b) They occur only as saprophytes. (c) They are less strictly dependent on hemoglobin. (d) They may have a coarser morphology. (e) They are slightly more difficult to keep in culture.

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\* From the Hospital of the Rockefeller Institute for Medical Research, New York.

1 Pritchett, Ida W., and Stillman, Ernest G. J. Exper. M. **29** 259, 1919.

2 Rivers, T. M. Bull. Johns Hopkins Hosp. **31** 50, 1920.

3 Stillman, Ernest G., and Bourne, Janet M. J. Exper. M. **32** 665, 1920.

4 Walker, J. E. J. Infect. Dis. **27** 618, 1920.

5 Rivers, T. M., and Leuschner, Erida, L. Bull. Johns Hopkins Hosp. **32** 130, 1921.

6 Bloomfield, Arthur L. Bull. Johns Hopkins Hosp. **32** 378, 1921.

7 Kristensen, Martin. Investigations Into the Occurrence and Classification of the Haemoglobinophilic Bacteria, Copenhagen, Levin and Munksgaard, 1922.

April 30 without benefit. On May 18, the discharge had completely subsided and was still absent on June 5, when the patient left school for his home after the winter term.

In Dr. H. G. Walcott's service, we have treated three patients having a clinical diagnosis of subacute catarrhal cholecystitis. It is interesting to note that in the bile of all these patients *B. pyocyaneus* has been isolated. These patients have been given a stock bacteriophage by duodenal tube in amounts varying from 15 c c to 50 c c. In these cases we have obtained complete relief of symptoms lasting from two to three months, but all of the patients have come back with their former symptoms, although not so marked. At present we are treating a series of children suffering from dysentery by the ingestion method, which will be reported later.

#### CONCLUSIONS

We have used the bacteriophage in a variety of cases. I believe the time is yet premature to draw elaborate conclusions regarding this method of treating infectious processes, however, it will be seen that in practically all of the cases described we have had some degree of success. The results are encouraging, but I do not feel that they warrant any broad statements at this time. We have administered the bacteriophage subcutaneously, by duodenal tube, into wounds, on dressings, by ureteral catheter, intranasally, intra-aurally and by ingestion in amounts varying from 1 c c to 50 c c. We have had no bad reactions other than in the two cases described in this paper. In a few instances, following the subcutaneous administration little "lumps" have formed under the skin in the subcutaneous tissue, which have been slightly painful but which have quickly disappeared. That the bacteriophage is harmless has been amply proved by the comparatively large amounts which we have given. Indeed in one case Davison gave over 1,300 c c without bad effects. These cases are not given as proof of cures, but as observations which lend encouragement for future work with the hope that such work will develop this new weapon for fighting infection, a weapon which holds enormous potential possibilities.

tion to the musical Over the aortic area the first sound was distinct, the musical murmur very faint, the second sound was pure No diastolic murmur was heard anywhere The rate was rapid, the rhythm regular

There was no dulness over the lungs Over the entire lower half of the chest posteriorly, and in the lower axillae on both sides were heard inspiratory and expiratory râles—sonorous, sibilant, and occasionally coarsely crackling Spoken and whispered voice sounds and tactile fremitus were normal

There was no tenderness over the abdomen The edge of the spleen, quite firm, was felt 1 cm below the costal margin The liver was not palpable

A few cervical and axillary superficial lymph glands were felt on each side There were no palpable epitrochlears

There was no vaginal discharge

There was no clubbing of the fingers, no pretibial edema and no petechiae anywhere on the body The skin everywhere was dry and coarse, in places suggestive of mild ichthyosis The left knee was slightly red over the patella, there was no tenderness, pain on motion or swelling The other joints were normal

The elbow, knee and ankle reflexes were active and equal on both sides \*There was a crossed Babinski sign

The results of blood culture are given in Table 1 The leukocyte count was 16,260 The differential count was lymphocytes and large mononuclears, 15 per cent, transitionals, 14 per cent, polymorphonuclear neutrophils, 68.7 per cent, polymorphonuclear eosinophils, 1.3 per cent, unclassified, 1 per cent The erythrocytes were pale, but otherwise normal

In the urine was found a trace of albumin, no sugar, a few red blood cells and a few white blood cells

The stereoscopic roentgenogram of the chest showed that for a child of her age, the lungs showed rather marked linear shadows extending, fanlike, from the hilus The apices were clear There was no indication of pulmonary infarction The 2-meter plate showed a generalized enlargement of the heart The transverse diameter was 12.5 cm, the longitudinal diameter, 13.5 cm The area of the heart was 101.3 sq cm and the angle 40 degrees

*Course of Disease*—On November 9, the general condition was unchanged The patient was still coughing She was quite drowsy Typical petechiae were seen in the morning as follows one in the left lower conjunctival sac, several on the buccal mucous membrane and one on the chest There was no sternal tenderness

In the third interspace just to the left of the sternum the first sound was loud and slapping, resembling that heard in mitral stenosis In the first space to the left of the sternum was heard a soft, blowing systolic murmur There were no irregularities in rhythm

There was no tenderness over the left knee The distal phalanx of the fourth right toe was tender, but not painful

Results of blood culture are given in Table 1

November 10 For the two preceding nights there had been profuse diaphoresis The preceding night the patient vomited twice, two and one-half and four hours, respectively, after supper, and again on the morning of the tenth, after breakfast The patient slept only in short naps during the night In the morning she was sleepy and irritable There was one petechial spot on the right buccal mucous membrane The right fourth toe was no longer tender There was superficial tenderness over the patella of the left knee, with an area of redness about 1 cm in diameter in its middle Movement of the joint was painless until it was flexed far enough to make tension on the skin over the patella The heart sounds were unchanged There was a small red subcutaneous spot showing through the skin over the palmar surface of the distal phalanx of the right ring finger, it was not tender

The leukocyte count was 22,400 The differential count was lymphocytes and large mononuclears, 14.6 per cent, transitionals, 17.4 per cent, polymorpho-

We shall record the following case, the first to be reported in which one of this group of organisms has been associated with a fatal pathologic process

#### REPORT OF A CASE

*History*—G W, an American school girl, aged 12, was admitted to the Hospital of the Rockefeller Institute for Medical Research on Nov 8, 1922, complaining of fever. Her family history was negative for rheumatism and heart disease. She had had uncomplicated measles and whooping cough at 3 years of age. For several years she had had periodic attacks of vertigo, preceded by vomiting, which were promptly relieved by lying down. She was usually kept in bed for one or two days following such an attack. In June, 1922 (five months before admission), she had had an attack of nausea and vomiting resembling an ordinary "dizzy spell." On going to bed the symptoms disappeared, and she felt well. Two days later she was taken to her family physician, who diagnosed "heart disease." He informed us that he heard a systolic murmur for the first time on that day, although he had examined her heart many times in preceding years. She was put to bed for two weeks and was seen by her physician several times. She had mild fever for a few days, the highest temperature being 102 F by mouth. During this period she had no pain, no shortness of breath, no cough and no swelling of the feet. At the end of the attack there was an appreciable pallor, enough to evoke comment by her friends, but in a few weeks her normal color reappeared and she returned to school feeling well in every way. She was able to climb two flights of stairs four times a day without breathlessness, palpitation or fatigue.

On Sept 25, 1922 (six weeks before admission), an attack began with nausea and vomiting, followed by a severe chill. The following day the only symptoms were slight nausea and anorexia. That day her physician repeated his diagnosis of "heart disease," and from that time observed, at each visit, a mouth temperature of 101 or 102 F. About two weeks before admission she began to have shooting pains in the left knee, without tenderness, pain on motion, or swelling. Later, on one or two occasions, there was observed tenderness over its mesial surface and also a spot of redness, about 4 cm in diameter, over the patella. There was never tenderness about the hamstrings or popliteal space. From the history, therefore, the existence of a true arthritis seems improbable. On Nov 1, 1922, she began to cough, the following day her temperature was found to be 103.5 F, and she was thought to be suffering from a mild bronchitis. The cough persisted until admission on November 8.

*Physical Examination on Admission*—The patient was a well developed, but poorly nourished girl, pale and not cyanotic. She lay quietly in bed, apparently free from discomfort. The skull and scalp were negative. The eyes were normal, no icterus or petechiae were present. The nose and ears were negative. In the mouth were several decayed teeth. The posterior pharyngeal wall was slightly reddened. The tonsils were not large. On the buccal mucous membrane were three small red spots, less than 1 mm in diameter, suggestive, but not typical, of petechiae. There were no cranial nerve palsies. The chest was symmetrical, both sides moved equally on respiration.

There was no precordial tenderness or cutaneous hyperalgesia. *Area of Cardiac Dulness*. In the second space, it extended 2.5 cm to the right from the midline and 4 cm to the left, in the third space, 3 cm to the right and 6 cm to the left, in the fourth space, 8.5 cm to the left, in the fifth space stomach tympany was present. The point of maximum impulse was in the fourth space, 6.5 cm to the left of the midsternal line. At the apex, the first sound was replaced by a high-pitched, musical murmur, which was followed immediately by the second sound. As the stethoscope was moved upward and to the right, the first sound became audible in the third space, just to the left of the sternum. It was followed by a systolic murmur which had a blowing quality in addi-

*Blood Cultures*—Blood from which cultures were to be made was withdrawn from a vein at the bend of the elbow into a graduated syringe, carried to the laboratory and inoculated at once. No anticoagulant was used. The bacteriologic data are tabulated in Table 1. Unless otherwise noted, the cultures were aerobic. All were incubated at 37 C and examined each day for evidence of growth.

No growth occurred in any of the anaerobic cultures, and growth in the first generation of the aerobic cultures was slow, becoming visible to the naked eye on

TABLE 1—*Blood Cultures*

Culture Number	Date	Quantity of Blood Inoculated	Medium	Result
W 25	Nov 8 6 15 p m	Approximately 15 cc	Dextrose agar plate, after setting the plate was covered with a tubeful of plain agar	5 colonies after 4 days' incubation
		Approximately 15 cc	Dextrose agar plate, after setting the plate was covered with a tubeful of plain agar	3 colonies after 4 days' incubation
		Approximately 3 cc	50 cc dextrose broth	Clouding after 2 days' incubation
		Approximately 5 cc	150 cc dextrose broth	Clouding after 2 days' incubation
W 26	Nov 9 4 30 p m	Approximately 1 cc	Dextrose agar plate	2 colonies after 4 days' incubation
		Approximately 1 cc	Dextrose agar plate	No growth
		Approximately 1 cc	Plain agar plate	No growth
		Approximately 15 cc	Dextrose agar deep tube	No growth
		Approximately 15 cc	50 cc dextrose broth	Clouding after 3 days' incubation
		Approximately 3 cc	50 cc dextrose broth	Clouding after 3 days' incubation
W 30	Nov 13 11 30 a m	Between 0.5 cc and 15 cc	Dextrose agar plate, after setting covered with a tubeful of dextrose agar	36 colonies after 4 days' incubation
		Between 0.5 cc and 15 cc	Plain agar plate, covered as above	20 colonies after 4 days' incubation
		Between 0.5 cc and 15 cc	Plain agar plate, covered as above	5 colonies after 4 days' incubation
		Between 0.5 cc and 15 cc	3 plain agar plates placed in Brown anaerobic jar, examined on 2d and 7th days	No growth
		2 cc	50 cc dextrose broth	Granular growth at bottom after 3 days
		4 cc	150 cc dextrose broth	Granular growth at bottom after 2 days
		3 cc	100 cc flask dextrose broth filled to the neck, containing piece fresh sterile potato	No growth
		3 cc	Same—petrolatum sealed	No growth
W 31	Nov 15 4 50 p m	1 cc	50 cc plain agar containing 5 cc ascitic fluid—2 large plates poured	No growth
		2 cc	50 cc plain agar containing 5 cc ascitic fluid—2 large plates poured	No growth
		5 cc	Added to 85 cc distilled water, centrifuged at high speed for 25 minutes, sediment taken up in 3 cc dextrose broth, added to 100 cc plain agar containing 10 cc ascitic fluid, 4 large plates poured	(One plate contaminated by surface spreader), no other growth

the third and fourth days of incubation in dextrose broth and on the fifth day in plates, the plates also showed a distinct increase in the colony count between November 8 and November 13, eight and three days, respectively, before death. In the plates, the colonies were very small, slightly greenish by transmitted light and surrounded by a small zone of clearing. After several transfers, surface colonies on freshly poured blood-agar plates became visible at the end of twenty-four hours. A more detailed study of this organism was made by Dr. Ernest G. Stillman, who reports: "The organism is a small, nonmotile, gram-negative



nuclear neutrophils, 65 per cent, polymorphonuclear eosinophils, 1 per cent, unclassified, 2 per cent. Urinalysis revealed a trace of albumin, no sugar, a few white blood cells, no red blood cells. She did not vomit after taking 0.3 gm chlorotone in the morning.

November 11 In spite of sedatives, codein and barbital, she had slept little. The unproductive cough continued. She complained of bilateral frontal headache. There was no tenderness on pressure over the frontal sinuses or antrums. There were two new petechiae in the right conjunctiva and several in the mouth, none could be seen on the skin, but they might readily have been obscured by the hyperkeratosis. Heart. No thrill was palpable. The musical quality of the systolic murmur had changed to a high-pitched, whirring sound, loudest over the third and fourth interspaces just to the left of the sternum, slightly roughened over the pulmonic area. The pulmonic second sound was accentuated. The action was still rapid and regular. The condition of the lungs was the same as on admission.

November 12 The patient slept much during the day, but was restless at night. The only change in her physical condition was an increase in the intensity of the first and second heart sounds, a more forceful precordial impulse and increased redness of the skin over the left patella.

November 13 The patient's condition was unchanged. The results of blood culture are given in Table 1. There were 15,860 leukocytes. The differential count revealed lymphocytes and large mononuclears, 16 per cent, transitional cells, 14.7 per cent, polymorphonuclear neutrophils, 67.1 per cent, polymorphonuclear eosinophils, 0.6 per cent, polymorphonuclear basophils, 0.3 per cent, unclassified, 1.3 per cent. The erythrocytes showed a distinct basophilic stippling and moderate anisocytosis.

November 15 On November 14, 4 gm of neocinchophen (0.13 gm per kilogram body weight) were administered by mouth without any effect on the temperature. The only symptom of drug action was increased perspiration, which had been fairly marked every afternoon and evening. On the morning of November 15, the patient looked a little worse—paler. There was one new petechial spot in the mucous membrane of the mouth.

There was less tenderness over the left patella, no new areas of tenderness had developed in the fingers or toes, and none over the sternum or ribs. In the fourth interspace just below the nipple, was heard a murmur which resembled a presystolic crescendo. The rate was very rapid, the rhythm regular. The whirring sound was heard only in the lower precordium. In the pulmonic area the blowing murmur was a trifle louder and rougher than on the preceding day. The results of blood culture are given in Table 1.

Urinalysis revealed a trace of albumin, a few red blood cells and a few white blood cells.

November 16 On the preceding day the patient received 4 gm of neocinchophen. It was her birthday, but she showed no interest in gifts or a party which was arranged for her. In the morning of November 16 she looked appreciably worse, the pallor had increased and was extreme. There were no new petechiae. She was clear mentally. Both radial pulses were imperceptible. The only change in the heart murmurs was that the first sound had lost its slapping character. There was dulness over both bases of the lungs with sonorous and sibilant râles. There were no crepitant râles. The reflexes were brisk. The crossed Babinski sign was still present. There was little tenderness over the left patella this morning, the redness had decreased.

The blood film revealed very pale erythrocytes, marked basophilic stippling, moderate anisocytosis and poikilocytosis.

8.30 p. m. The condition remained unchanged until about 8 p. m., when the attendant noted an alteration in the breathing. A few minutes later the patient was unconscious, and in Biot's respiration, the precordial impulse was imperceptible, the knee reflexes were still present. The Babinski sign was absent. There was no muscular contraction. Respirations continued for several minutes.

The aneurysm of the abdominal aorta, found postmortem, was entirely unsuspected clinically.

bacillus in being hemolytic *B. pertussis* and the Morax-Axenfeld bacillus are not true hemophils. The hemolytic hemophilic bacillus, described by Davis,<sup>9</sup> grew much better under anaerobic than under aerobic conditions, and failed to grow at room temperature.

The organism described falls, therefore, into the group of hemolytic hemophilic bacilli. Whether this group should be classified with the influenza bacilli or set apart by itself is an academic question which cannot be dealt with in this paper.

**Agglutination**—The organism was agglutinated by the patient's serum in dilutions of 1:160. Serums obtained on November 9 and November 13 were used.

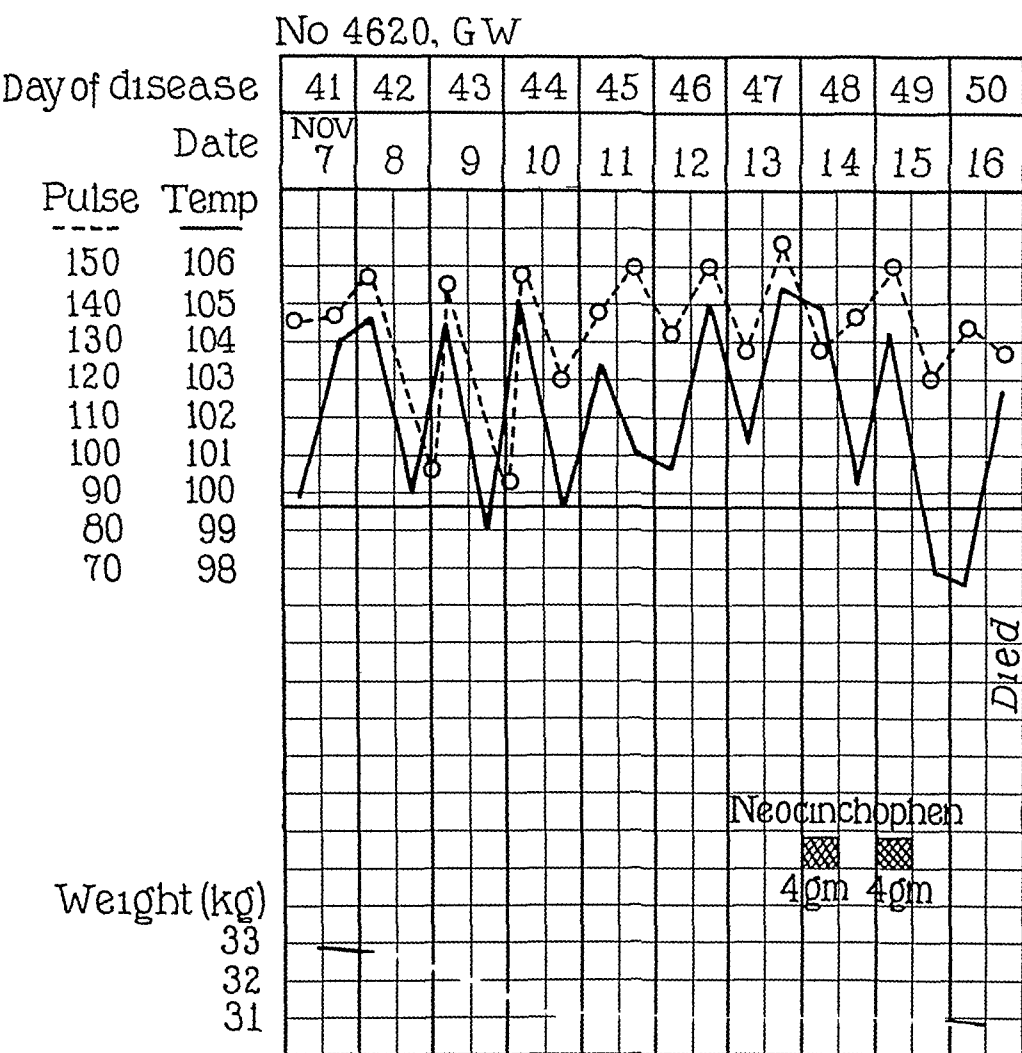


Fig. 1—Pulse rate and temperature of patient while in hospital

**Technic**—A satisfactory suspension of organisms was obtained by resuspending in 20 c.c. of plain broth the centrifuged sediment of a twenty-four-hour blood extract-broth culture (50 c.c. plain broth containing 0.5 c.c. blood extract prepared according to the method recommended by Wollstein). Serum dilutions were made in plain broth, to each 0.5 c.c. of the mixture was added 0.5 c.c. of the suspension of organisms. The agglutinations were made in duplicate, one set incubated at 37° C., the other at 55° C. At the end of three hours they were read, placed in the refrigerator and read again the following morning. Only the final readings are recorded (Table 3).

bacillus which takes the counterstain deeply and exhibits varying degrees of pleomorphism. Some of the rods in eighteen-hour blood broth cultures show definite beading and bipolar staining. Surface colonies after eighteen hours' incubation on rabbit blood agar appear as small, almost pin-point elevations surrounded by a definite zone of true hemolysis. Hemolysis occurs also around the deep colonies. After thirty-six hours they vary from 1 to 2 mm in diameter, and have an opaque, yellowish center surrounded by a transparent, slightly serrated border. The organism grows readily in blood broth, causing no hemolysis, but producing a dark yellowish green color in the supernatant fluid after a few days. On the other hand, growth is initiated with difficulty in subcultures on blood agar plates. It did not grow on sheep serum agar, ascitic agar, or glucose agar, on oleate agar it grew poorly. In Dunham's peptone solution enriched with 2 per cent blood

TABLE 2—*Necropsy Cultures, Nov 17, 1922*

Num ber	Material	Medium	Result
W 32	About 0.3 c.c. blood with drawn from right auricle	5 c.c. dextrose broth tube	No growth
	1.5 c.c. blood withdrawn from the left ventricle	Dextrose agar plate	Many colonies on 3d day—pure culture, same organism recovered from blood during life
	About 1 c.c. blood with drawn from left ventricle	5 c.c. dextrose broth tube	Clouding on 4th day—pure culture, same organism
W 33	Pus from sphenoid sinus	Streaked on freshly poured dextrose blood agar plate	Heavy growth, only one type of colony—pneumococcus, Group 4
	Pus from sphenoid sinus One loopful	5 c.c. dextrose broth	No growth

TABLE 3—*Agglutination*

Final Serum Dilution	Patient's Serum, November 9		Patient's Serum, November 13		Control Normal Human Serum		Broth Control (No Serum)	
	Incu- bated at 37 C	Incu- bated at 55 C	Incu- bated at 37 C	Incu- bated at 55 C	Incu- bated at 37 C	Incu- bated at 55 C	Incu- bated at 37 C	Incu- bated at 55 C
1 10	++++	+++	++++	++++	±	±		
1 20	++++	++++	++++	++++	—	—		
1 40	++++	++++	+++	+++	—	—		
1 80	++++	++++	++	++	—	—		
1 160	++++	++++	++	++	—	—		
1 320	++	++	—	+	—	—	—	—
0								

extract<sup>8</sup> the growth was luxuriant. Using this as a substrate, acid was produced in glucose, galactose and maltose, but not in levulose, saccharose, lactose or mannite. It did not produce gas. The final hydrogen-ion concentration in Dunham's peptone solution containing glucose and blood extract was  $p_H$  6.2. It did not produce indol. Five-tenths cubic centimeter of an eighteen-hour culture failed to kill white mice and guinea-pigs. In blood broth it remained viable for two weeks at icebox and at room temperature."

This organism can be readily differentiated from such other small, nonmotile, gram-negative bacilli as *B. mallei*, *B. abortus*, *B. melitensis*, *B. pestis* and *B. tularensis* by its inability to grow in mediums not containing blood or blood extract. It differs from *B. influenzae*, *B. hemoglobinophilus-canis* and the Ducrey

<sup>8</sup> Blood extract was prepared according to the method recommended by Wollstein, Martha J. J. Exper. M. **30** 555, 1919.

embolic myocarditis, glomerular nephritis, multiple infarcts of the spleen, kidney and heart, dissecting aneurysm of the abdominal aorta, multiple petechiae in the skin, conjunctivae, buccal mucous membrane, pleurae and meninges, acute localized meningitis, ascites and hydropericardium, bilateral sphenoiditis and ethmoiditis (pneumococcus, Group 4)

There was marked pallor, good physical development and poor nutrition

The precordial area was small, there were no pleural adhesions. There were a few petechiae on the visceral pleura. The pericardial cavity contained about 60 cc of clear, serous fluid, grossly, the pericardium was normal.

The heart weighed 240 gm. The musculature was pale, mottled and non-friable, the vessels stood out as reddish dots. The left ventricle measured 1.4 cm,

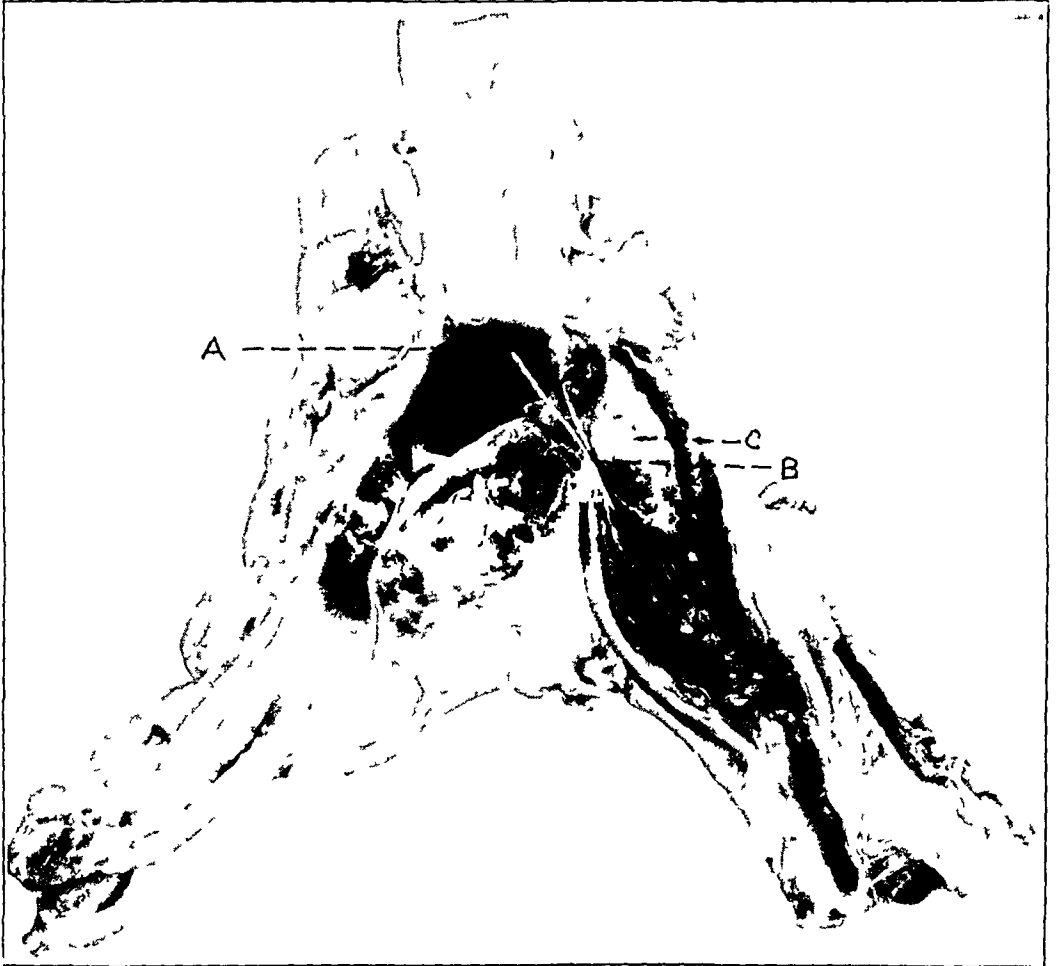


Fig 3—The aorta at its bifurcation into the common iliacs, dorsal aspect. *A* indicates the large aneurysmal orifice, *B*, the lumen of the right iliac artery indicated by the straw and encroached on by the aneurysmal contents, *C*, the dissecting aneurysm in the wall of the right common iliac.

the right ventricle 0.4 cm in thickness. The opened mitral valve measured 8 cm. On the aortic cusp was an irregular, pale, pink vegetation, which measured 2.4 by 1.8 by 1 cm, only slightly friable and firmly attached to the free edge. It involved the chordae tendineae, but did not extend for any appreciable distance onto the auricular surface of the valve. There was a small aperture in the vegetation at its attachment to the valve edge. Elsewhere this cusp showed no gross lesion. On the nonaortic leaflet anteriorly there was a smaller, irregular, tongue-like vegetation measuring 4 mm in diameter. The remainder of this cusp showed a row of thickly deposited, fairly adherent verrucae along its line of

SUMMARY—A diagnosis of "heart disease" was made in the case of a school girl, 12 years old, who five months before admission to the hospital had an attack of fever lasting two weeks without other symptoms. Three and a half months later she had a second attack of fever with progressive anemia terminating in death on the fiftieth day. She was in the hospital for nine days. There was a systolic murmur of varying quality. Superficial tenderness over one patella, tender finger tips and toes, petechiae in the skin, conjunctiva and oral mucosa



Fig 2—The heart opened to expose the mitral valve and vegetation, *A*, the smaller vegetation on the nonaortic cusp with adjacent row of verrucae

were present. The spleen was palpable. Moderate leukocytosis and low grade hematuria were present. The patient had bacteremia, increasing in intensity during the last week of illness, and a gram-negative hemolytic hemophilic bacillus was isolated. This organism was agglutinated by the patient's serum in 1:160 dilution.

*Postmortem Examination*—The anatomic diagnosis was vegetative and verrucose mitral endocarditis, septicemia (a hemolytic hemophilic bacillus), focal

bulged into the lumen of the artery, which was considerably narrowed. The anterior wall of the left iliac artery showed a superficial ulceration 1 cm in diameter just below the aneurysmal orifice (Fig 3).

The peritoneal cavity contained about 300 cc of clear, straw colored fluid. The tip of the spleen extended 2 cm below the left costal margin. The other viscera were normally disposed. The mesenteric glands were moderately enlarged, but on section appeared intact.

The spleen weighed 340 gm. The capsule was adherent to the diaphragm by fine, easily broken adhesions. Its color was brick red, and old and recent infarcts were seen. On section the surface was bright red and firm, the malpighian corpuscles appeared moderately enlarged. There was a yellow, wedge-shaped, fairly firm, infarcted area, 2 cm in length, at the inferior pole, and more recent, less sharply defined, pinkish yellow infarcts on the anterior border.

The left kidney weighed 165 gm. The capsule stripped readily, leaving a smooth surface, except for large depressions over firm, yellow, infarcted areas. The cut surface was rather pale, the cortical markings were not distinct, but differentiation of cortex and medulla was obvious. Numerous irregular, firm,



Fig 5—A section of the periphery of the vegetation (indicated in Fig 3) showing the bacilli  $\times 1,000$

yellow infarcts were seen, one at its inferior pole was almost cartilaginous in consistency, and bright yellow. The right kidney weighed 150 gm and exhibited the same features.

Both knee joints contained a small amount of clear, viscid material resembling egg white. In the left was seen one small petechia on the synovial membrane between the condyles.

The bone marrow in the femur was abundant, grayish red, moderately soft, and seemed to contain little fat.

The brain appeared edematous and showed a few small petechiae on the lateral surface, and a reddened, suffused area, not definitely outlined on the medial aspect of the right hemisphere.

The internal ears were normal. The sphenoidal and posterior ethmoidal sinuses were filled with about 1 cc of very thick, tenacious, greenish gray pus, their exposed lining membrane appeared turbid and reddened. Smears of the pus stained by Gram's and Hiss' capsule stains showed many pus cells and encapsulated, gram-positive, elongated cocci in pairs. No gram-negative organisms were seen after prolonged search. The anterior ethmoidal and the frontal sinuses were normal.

The tonsils were not enlarged, on section they showed no evidence of disease.

closure, each was two or three times the diameter of the usual rheumatic verruca. Otherwise the valve did not appear unusually thickened, except for a few small, discrete, yellow plaques at the base of the aortic cusp and under the verrucae. The usual sclerotic thickening commonly seen on its aortic cusp was present but not accentuated (Fig 2).

The other valves showed no macroscopic lesions. The larger coronary arteries contained some loose clot, the intima was thin and smooth. The aorta showed fatty streaks throughout its whole length. At its bifurcation into the common

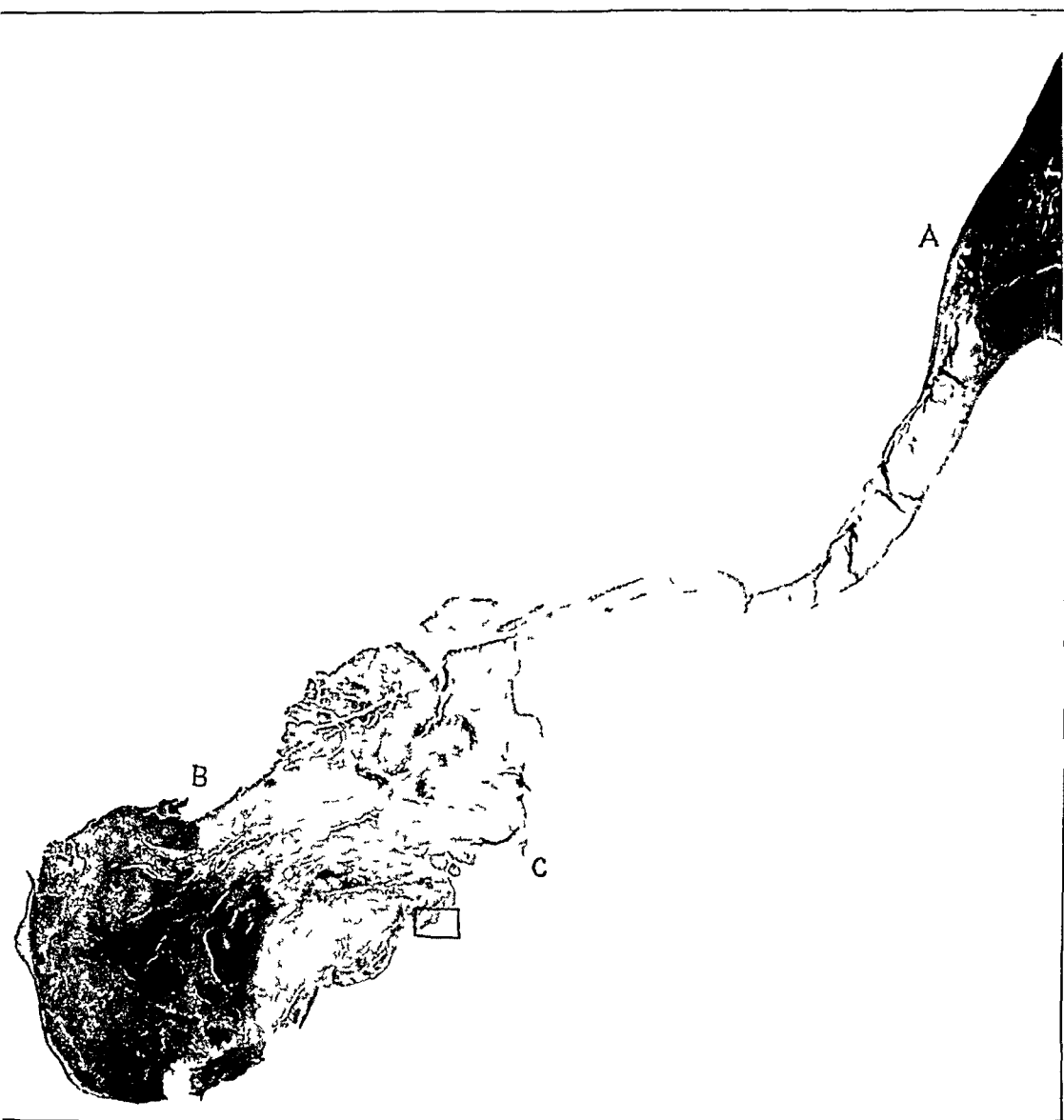


Fig 4—The vegetation on the aortic cusp of the mitral valve. *A* indicates the base of the valve, *B*, the vegetation, *C*, the origin of a chorda tendineae.  $\times 7$

iliacs there was an aneurysm on its anterior wall the size of a large walnut. On opening this from behind, a ringlike aperture, 1.5 cm in diameter, was seen, which connected with the aneurysmal sac and was filled with a red clot. This aneurysm extended down the right iliac, dissecting between the intima and media and re-entering the artery at a point 1.5 cm below the bifurcation. The aneurysm

The myocardium was studded with infarcts, some almost the size of a low-power field (Fig 6), there were also perivascular areas of focal, embolic, exudative myocarditis rich in polymorphonuclear leukocytes. These areas were in close relationship with capillaries and larger vessels which were filled with cellular and fibrinous thrombi containing polymorphonuclear leukocytes in predominance (Fig 7). The thrombotic process in the same section could be traced in series from the very cellular clot, above described, containing bacteria, to vessels showing a fibrous stenosis. The infarcted areas, however, more numerous than the inflammatory lesions, consisted of edematous tissue in which muscle fibers had disappeared and only the framework remained. The periphery of such areas was being invaded by newly formed capillaries and fibroblasts, and there was some hemorrhagic extravasation, the contiguous muscle fibers were either vacuolated or appeared homogeneous without striations or nuclei. In the remaining unin-



Fig 7—Inflammatory process in the myocardium of the left ventricle. *A* indicates a thrombus in the arteriole, *B*, thrombosed capillary, *C*, focal exudative perivascular lesion.  $\times 150$

involved myocardium the fibers were small with distinct striations and normal nuclei.

The pericardium and mural endocardium were intact.

The contents of the aneurysm consisting of cells and debris with little fibrin, lay mostly between the adventitia and media, but in some places broke through the intima to the surface. The intima of the aorta above the lesion was intact, and there were no signs of emboli in the adventitial vessels, while the intima near the aneurysmal orifice was irregularly thickened.

The pulp tissue in the spleen was atrophic throughout, but was invaded by numbers of polymorphonuclear leukocytes, the sinuses were congested. Bland infarcts of irregular size and shape were seen. The malpighian corpuscles were small, their blood vessels were uninvolved, and there were hyaline-like deposits in their centers.



*Microscopic Examination*—The tissues were fixed in Zenker's solution (with acetic), solution of formaldehyd USP 10 per cent, Pianesc's solution and alcohol. The routine stains were eosin and methylene blue or hemotoxylin and eosin, Giemsa, Gram's, Weigert's elastic tissue, Weigert's fibrin, and Mallory's connective tissue stains were employed where required.

Sections taken from the uninvolved portion of the mitral valve showed nothing of note except a localized fibrous thickening in one area. The earliest small verrucae were formed by a marked localized proliferation of fixed tissue cells,

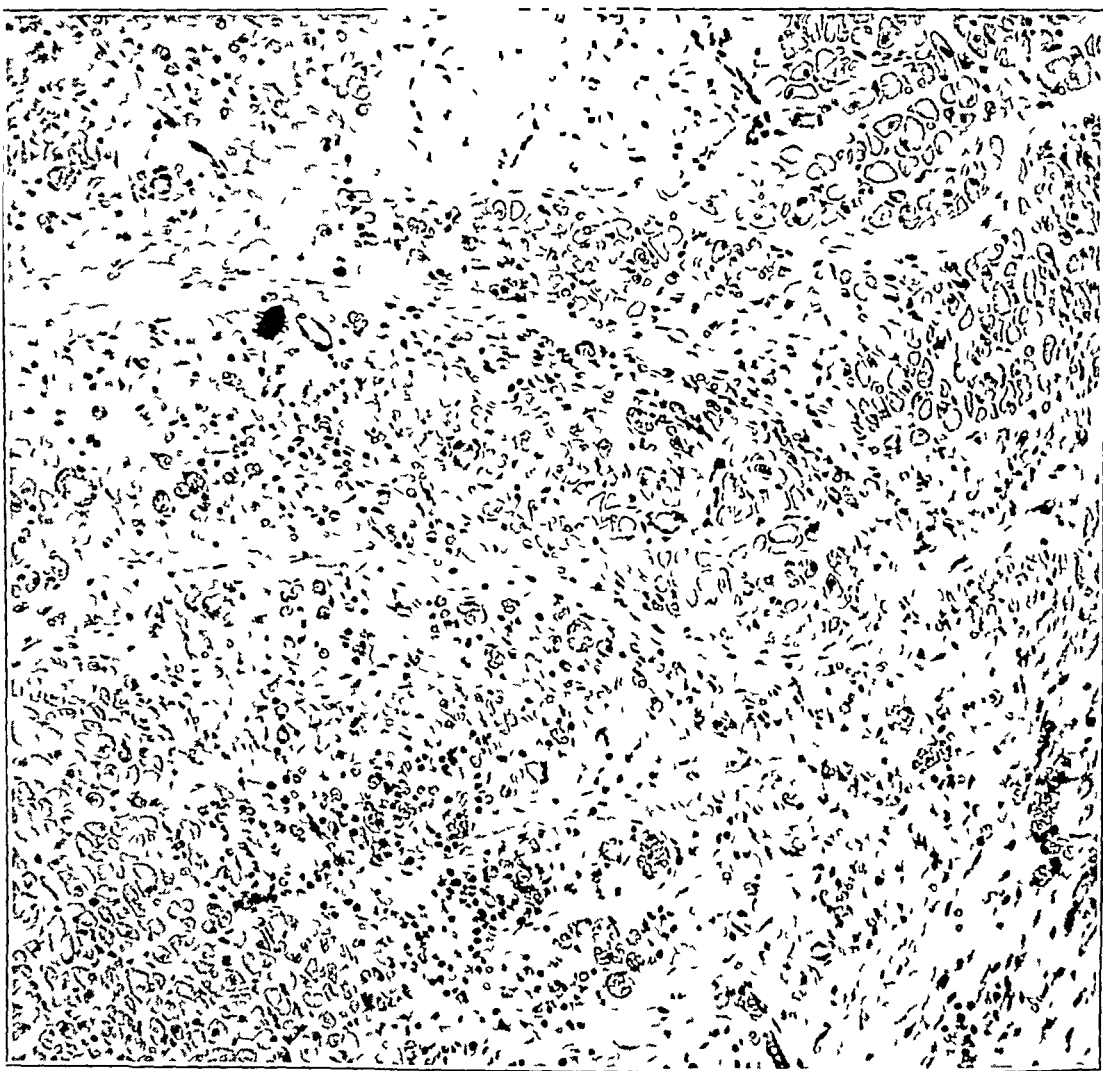


Fig 6—An infarcted area in the myocardium of the left ventricle  $\times 150$

with small fibrinous deposits on the surface, over which the endothelium was missing. Many small vessels were seen in the neighborhood of the verrucae. The large vegetation was attached for a short distance to the free edge and also to the inferior surface of the cusp. A few gram-negative bacilli were noted in the valve itself, and many in the vegetation. At its junction with the valve was an area of active fibroblastic proliferation with few migratory cells (Fig 4). No vascular thrombi were noted. The vegetation itself was composed of laminated fibrin, debris, red and white blood cells, and masses of bacteria occurring chiefly along the periphery (Fig 5).

The tubules of the kidney were comparatively well preserved and contained many cellular casts. Irregular bland infarcts of varying microscopic sizes were seen surrounded by zones of fibrous tissue, the precapillary vessels in the vicinity showed fibrin plugs. Around many of the glomeruli there was an infiltration of polymorphonuclear leukocytes and round cells which extended in some places between the neighboring tubules and in other places involved the whole glomerular tuft. Intertubular infiltration was seen only in the region of inflamed glomeruli (Fig 8). In certain glomeruli individual capillary loops were plugged with fibrin, while the remaining loops in the same glomerulus appeared normal. A few glomeruli were noted in which a segment of the capillary tuft had undergone hyalinization and fusion with Bowman's capsule (Fig 9). Complete hyalinization of glomeruli was seen only in or near the larger kidney infarcts.

Tonsils, lymph glands, bone marrow and other organs showed no pathologic lesions.

#### COMMENT AND SUMMARY

In the case described there was a typical clinical picture of subacute bacterial endocarditis of fifty days' duration. The only illness which might have led to previous valve injury was a short attack of fever three and a half months before the onset of the final illness. The pathologic picture also closely resembled that described in other forms of subacute bacterial endocarditis. Of particular interest was the presence in the kidney of both types of lesions associated with this disease, namely (a) small infarctions of segments of glomerular tufts, described by Loehlein<sup>10</sup> and by Baehr,<sup>11</sup> and (b) a glomerulonephritis. Libman<sup>12</sup> has never found the form lesion in his *B. influenzae* cases, in which glomerulonephritis was frequent.

At necropsy the purulent ethmoidal and sphenoidal sinusitis was the only infective process found which might have antedated the endocarditis and served as a portal of entry, but the pus from the sinuses, in films and cultures revealed no gram-negative bacilli, only pneumococci (Group 4).

The bacterium recovered from the blood is a member of the family of hemophilic bacilli, differing from influenza bacilli in being hemolytic and comparatively avirulent, in fact, it has never before been reported as occurring in a definitely pathogenic capacity. The proof of its etiologic rôle in this case rests on the following evidence: its isolation in pure culture from the blood on three occasions during life and also at necropsy, the occurrence of morphologically identical bacilli in microscopic sections of the vegetation and of the secondary embolic lesions, and the presence in the patient's serum of specific antibodies (agglutinins) against the organism.

A comparison of this bacterium with its more virulent relative the influenza bacillus, calls to mind a similar relationship existing between

10 Loehlein. *Med Klin* 6 374, 1910.

11 Baehr. *G. Am J M Sc* 144 327, 1912.

12 Libman, E. *Med Clin N America* 2 130 1918-1919.

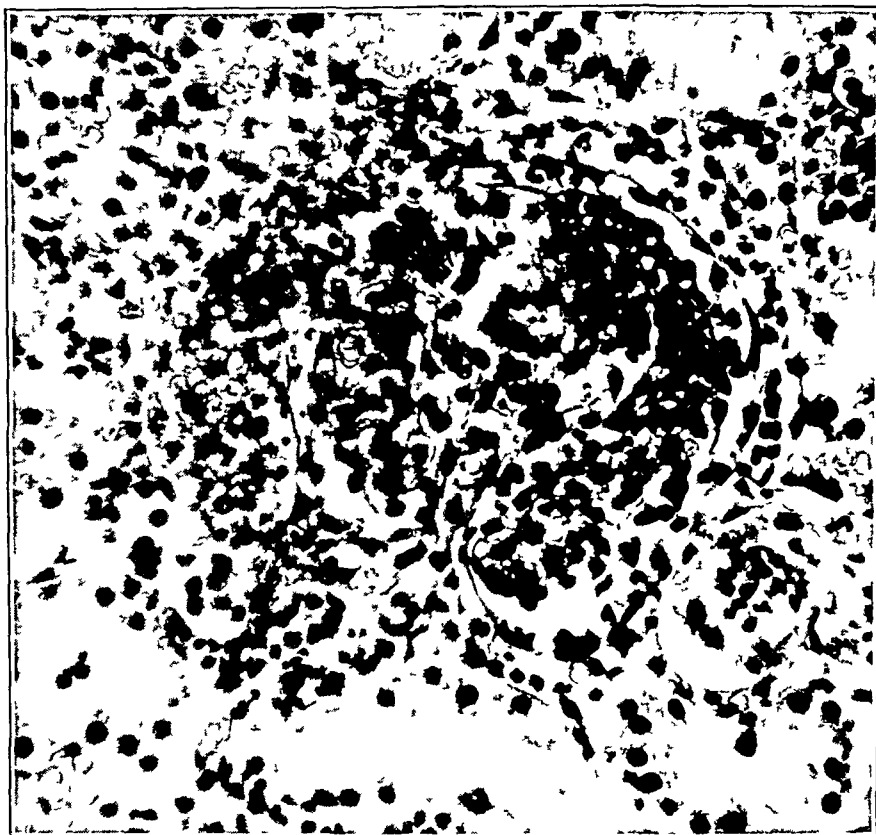


Fig 8—Kidney showing the focal glomerulonephritis  $\times 350$

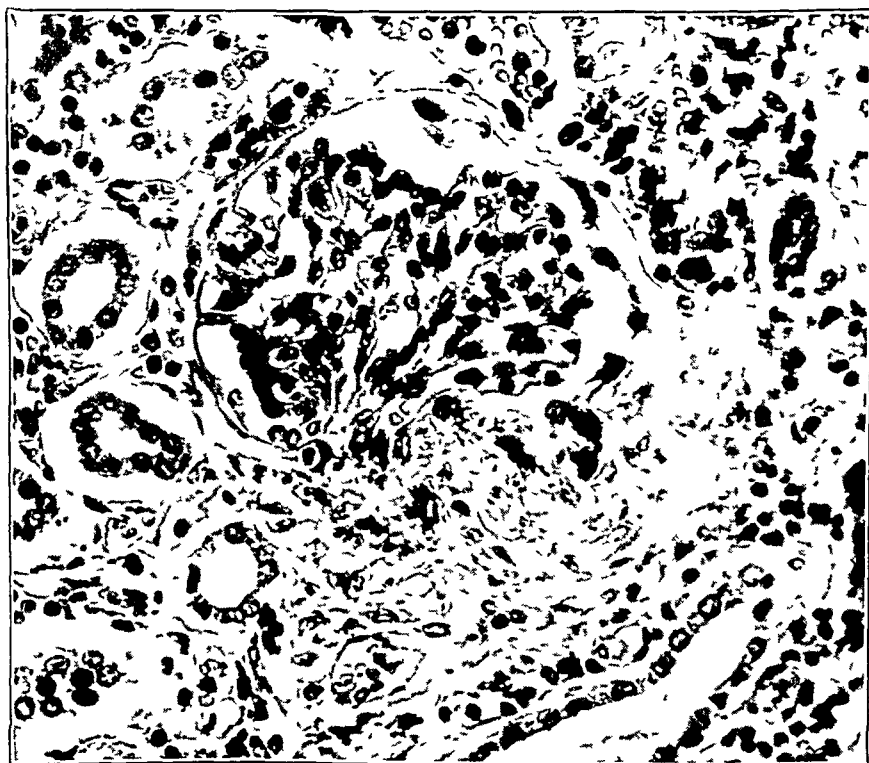


Fig 9—Kidney showing the infarction of a segment of a glomerular tuft  $\times 350$

# THE UREA CONCENTRATION FACTOR IN THE ESTIMATION OF RENAL EFFICIENCY<sup>1</sup>

I M RABINOWITCH, M D

MONTREAL, CAN

Results obtained by the application of the methods now in use in the study of renal function can, at best, show but an approximation of the truth, so far as the efficiency of the kidneys is concerned. The reason for this is obvious. The study of a pathologic reaction is the study of a disturbed physiologic reaction, and the exact physiology of the kidneys is far from perfectly understood. It is now well recognized that what we consider normal anatomic findings are not necessarily associated with normal functional findings, and vice versa. In the absence of certain specific renal stimulants or depressants, and by making the kidney excrete urea to its full capacity, Addis<sup>1</sup> has shown that deductions can be made from functional findings as to the quantity of tissue present. This author and his co-workers<sup>2</sup> have also shown that the kidney substance can excrete seven times the amount of urea ordinarily eliminated. It is therefore reasonable to assume that, normally, in the excretion of urea at least, the kidney tissue is being employed only to the extent of one seventh of its capacity. The general conception of nephritis, as well as of uremia, is undergoing a change from that held before renal efficiency tests became common practice. Some of the clinical signs and symptoms looked on previously as due to anatomic or functional disturbances of the kidney alone are now regarded by many as being due to a general disturbance in metabolism, and associated with, rather than due to, the nephritis. In spite of our incomplete knowledge, however, there is no doubt that the tests now in use have a definite clinical value, if in the interpretation of the results obtained proper consideration is given to the possible sources of technical errors involved in the biochemical analyses and the influence of extrarenal factors.

Practically all methods for determining kidney function now in use are based on the following generalization. When the kidneys become unable to properly excrete the end-products of metabolism, these must either be more slowly excreted than normally or accumulate in the blood, and the degree of retention of these substances in the blood or their rate of excretion in the urine is an index of the degree of impair-

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\* From the department of metabolism of the Montreal General Hospital

\* This work was done with the aid of a grant from the Cooper Memorial Fund

1 Addis, T. Renal Function and the Amount of Functioning Tissue, *Arch Int Med* **30** 378 (Sept.) 1922

2 Addis T., Sheeky, A. E., and Bevier. *Am J Physiol* **46** 11 (April) 1918

nonhemolytic streptococci (*Streptococcus viridans*) and hemolytic streptococci *Streptococcus viridans*, usually less virulent than *Streptococcus hemolyticus*, is the common causative agent in subacute bacterial endocarditis, but also occurs commonly as a saprophyte in the throat, the site from which these hemolytic hemophilic bacilli have heretofore been exclusively recovered

excretion of solids<sup>8</sup> this is indirectly recognized by accepting the data obtained only when associated with a definite diet. Other factors than renal which may frequently cause an increase in the amount of non-protein nitrogenous constituents of the blood have been pointed out. These include acute pancreatitis, general peritonitis, intestinal obstruction<sup>9</sup> and lethargic encephalitis<sup>10</sup>. Even where the retention of nitrogen is due to renal disorder alone, the correlation of the clinical picture with the laboratory data is of importance in distinguishing between temporary and permanent disturbances. In many urologic conditions associated with retention of urine, the prognostic significance of the renal function tests can only be appreciated by estimating the relative importance of extrarenal and renal factors<sup>11</sup>. The possible sources of error in the interpretation of the results of the urea (urine) concentration test have been pointed out by the authors of the test<sup>5</sup>. The writer has shown the effects of delayed absorption of urea from the alimentary tract<sup>4</sup>. What has probably not been sufficiently emphasized is the necessity of performing the test under standard conditions. Many results not consistent with the clinical picture were frequently encountered in this hospital before standard conditions were adopted. This routine is employed. The patient is allowed no food or fluids of any kind after 6 p. m. the evening before the test. At 6 a. m. on the day of the test the patient voids. This specimen is discarded. The urea is then given as described by the authors of the test, and the urine is collected at 7 a. m. and 8 a. m. The performance of the test in this manner interferes least with the patient's comfort, conforms best to the hospital routine, does not interfere with meal hours, and at the same time avoids the possibility of the patient receiving any food or drink preliminary to the test. The necessary precautions described by the authors of the test, discarding tests which produce diuresis, etc., are strictly observed.

When the renal lesion is associated with an impairment in the excretion of nitrogenous substances the application of urea studies in the estimation of renal efficiency probably, as the data here show, excels all other methods. A consideration of some of the aspects of our present knowledge of urea metabolism well emphasizes this point of view. Urea is a normal end-product of protein metabolism and in the

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8 Sharlit, H, and Lyle, W. G. A New Method of Interpretation of the Renal Function Test Meal, *Arch. Int. Med.* **28** 649 (Nov.) 1921.

9 Rabinowitch, I. M. The Prognostic Value of the Study of the Blood Chemistry in the Acute Abdomen, *J. Canadian M. A.*, March, 1921.

10 Umber, F. Mesencephalitis epidemics, *Deutsch. med. Wchnschr.* **47**:261, 1922.

11 Rabinowitch, I. M. The Prognostic Value of the Study of the Blood Creatinine in Nephritis, *J. Canadian M. A.* May, 1921.

ment of renal efficiency Attempts to give mathematical expression to the estimation of the work done by the kidneys in concentrating substances from the weak dilution in which they are found in the blood to the greater concentration in which they are found in the urine, were first made by Dreser in 1892<sup>3</sup> Since then the increasing number of factors which influence such calculations have been recognized, and the general consensus of opinion now is that our knowledge of the total work done by the kidneys is still imperfect Clinically, this is only too well emphasized In a detailed study of kidney function made in this hospital<sup>4</sup> it was shown that various types of nephritis show various responses to the same test, and therefore no one test for kidney function can be used to the exclusion of all others for the purpose of renal diagnosis

The biochemical methods in general use for studying the various renal lesions associated with impaired excretion of nitrogenous substances are the Mosenthal modification of the Hedinger and Schlayer renal test meal, the excretion of solids and phenolsulphonephthalein, the estimation of the amount of nonprotein nitrogen in the blood, including urea, uric acid and creatinin, and the urea concentration test of MacLean and de Wesselow<sup>5</sup> The technical difficulties previously encountered in these tests have been practically eliminated by improved biochemical methods In all these tests the interpretation of the results is complicated by extrarenal factors The possible influence of such factors in the renal test meal have been pointed out by Mosenthal in his original<sup>6</sup> and in subsequent articles In the study of the excretion of solids, the methods generally employed include the determination of the specific gravity of the urine That the specific gravity is no real quantitative index of the total concentration of solids has been known by physical chemists for a long time Judging from the general application of the specific gravity in estimating solids, this is, however, not generally recognized clinically Two solutions, one containing urea and the other salt or sugar, and each having the same number of grams per liter, will not have the same specific gravity Recently this has been given clinical consideration<sup>7</sup> In the common method of studying the

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3 Dreser, in Cushny, A R Monograph on Physiology The Secretion of Urine, New York, Longmans, Green & Company, 1917 Lea & Febiger

4 Rabinowitch, I M A Study of the Urea Concentration Test for Kidney Function, Arch. Int. Med. **28** 627 (Dec.) 1921

5 MacLean, H, and de Wesselow, O L V On the Testing of Renal Efficiency with Observations on the Urea Coefficient, Brit J Exper Path **1** 53 (Feb.) 1920

6 Mosenthal, H O Renal Function as Measured by the Elimination of Fluid Salt and Nitrogen and the Specific Gravity of the Urine, Arch Int Med **16** 733 (Nov.) 1916

7 Addis, T, and Foster, M G The Specific Gravity of the Urine, Arch Int Med **30** 555 (Nov.) 1922

blood urea, but, as Harrison<sup>15</sup> pointed out, "did not definitely advocate the simple expedient of combining the two tests and thus simultaneously checking the urea concentration (urine) and standardizing the blood urea" Unfortunately, Harrison, as he himself states, in applying this principle, was unable to give normal values. Harrison accepted normal urea concentration factor values from a study of all patients having a urine urea concentration of over 2 per cent. The urea concentration factor  $\frac{\text{mg urea per 100 c c urine}}{\text{mg urea per 100 c c blood}}$  shows that such findings do not necessarily indicate a normal efficiency of the kidney. Accepting as normal a urine urea concentration of 2 per cent or over, when found two and one half hours after the ingestion of 15 gm urea, the lowest blood urea concentration at this period was 37 mg and the highest 133 mg per 100 c c. The normal values of the urea concentration factor were lowest, 18 mg, and highest, 72 mg. The maximum increase in the concentration of blood urea over that present before administration of urea was 58 mg. Analysis of all these data shows that in only one case could the patient be regarded as free from any renal lesion—that in which the urea concentration factor was 72. The other data quoted above were obtained from patients having lesions, including chronic nephritis, calculus of the right kidney and unilateral malignant tumor of the kidney. Qualitatively, the results obtained, however, had definite significance.

The data recorded in this hospital are based on the study of 200 cases, in all of which there were renal lesions associated with ozotemia or other evidence of a disturbance in the excretion of nitrogenous substances. A study was made of the value of the estimation of the urea concentration factor as a test for renal efficiency as compared with the other test commonly in use.

*Technic*—In all the urea estimations of the blood and, with only few exceptions of the urine the Van Slyke urease method was used. In the few instances in which the hypobromite principle was applied, the Stehle<sup>16</sup> method was used with the Van Slyke carbon dioxide apparatus. A possible source of error in the urease method which appears to be worth recording is the fact that at times the activity of the urease preparation may be impaired, thus yielding low urea values. All urea determinations should be carried out in duplicate, and the activity of the urease constantly gaged by a control consisting of a urea solution of known concentration. When protein is present in the urine in excess of 0.4 per cent, this should be removed where the hypobromite principle is applied. Harrison describes a simple procedure for this purpose with the use of salicyl-sulphonic acid.

A great advantage of urea estimations over the various dye tests is that pus, blood, bacteria and urinary pigments do not interfere with the results.

15 Harrison, G. A. On Urea Tests of Renal Function, *Brit J Exper Path* 3 28 (Feb) 1922

16 Stehle, R. L. The Gasometric Determination of Urea in Urine, *J Biol Chem* 47 13, 1921



average adult on an average diet constitutes about 80 to 90 per cent of the total nitrogen eliminated in the urine in twenty-four hours. Unlike some other urinary constituents, a great deal of work must be done by the kidney in excreting urea. The energy used by the kidney in excreting urea can be calculated according to known physical principles by applying the Vant Hoff theory of solutions. Further proof of the great amount of work the kidney must do to excrete urea is furnished by the experiments of Barcroft and Straub on the oxygen consumption of the kidney in relation to diuresis. There is a marked contrast between these results and those obtained with the diuresis due to Ringer's solution, water or sodium chlorid. Urea is uniformly distributed in all the organs and body tissues, including the blood.<sup>12</sup> An appreciation of this fact is important. The uniform diffusion of urea prevents osmotic pressure differences across the membranes of the body. This absence of osmotic pressure differences will therefore not influence the movement of the body fluids and therefore will be less likely to cause hydremia,<sup>3</sup> which is an important factor influencing renal excretion. Following the administration of urea it undergoes no chemical change, and normally its rate of elimination is rapid. When prevented from being excreted, it is all stored in the body, except traces which appear in the bile and sweat. Its rate of excretion is governed by its concentration in the blood. Diuresis following urea administration is due to kidney activity alone. Large amounts may be injected and followed by considerable diuresis, yet there may be no increase in the blood flow through the kidney. This is demonstrated in one of the experiments by Lamy and Mayers.<sup>13</sup> Besides the excretion of urea being chiefly a function of the kidneys, extrarenal factors causing high blood ureas or low urine urea concentrations are more easily excluded than factors which influence the other tests. The most common urea tests employed are (a) the estimation of the blood urea nitrogen, (b) the urine urea concentration test of MacLean and de Wesselow, and (c) Addis' ratio  $\frac{\text{Urea in one hour's urine}}{\text{Urea in 100 c c blood}}$ .

#### THE UREA CONCENTRATION FACTOR

That the function of the kidneys can be gaged approximately by the association of blood and urine studies has been recognized for a long time. The earliest attempt to do this has been by the application of the freezing point ( $\Delta$ ) studies to blood and urine. In 1921, MacLean<sup>14</sup> reported the principle of dividing the urine urea by the

12 Marshall, E. K., and Davis, D. M. Urea. Its Distribution and Elimination from the Body, *J. Biol. Chem.* **18** 53, 1914.

13 Lamy and Mayers, quoted from Cushny. *J. Physiol. & Path.* **8** 258, 1906.

14 MacLean, H. Discussion on Renal Efficiency Tests, *Brit. M. J.* **2** 245, 1921.

## DISCUSSION OF RESULTS

Albuminuria still remains the most frequent and certain sign of kidney lesions. It appears reasonable to assume that in the great majority of the cases studied—in all of which the patient had albuminuria—there must have been some functional changes. Since,

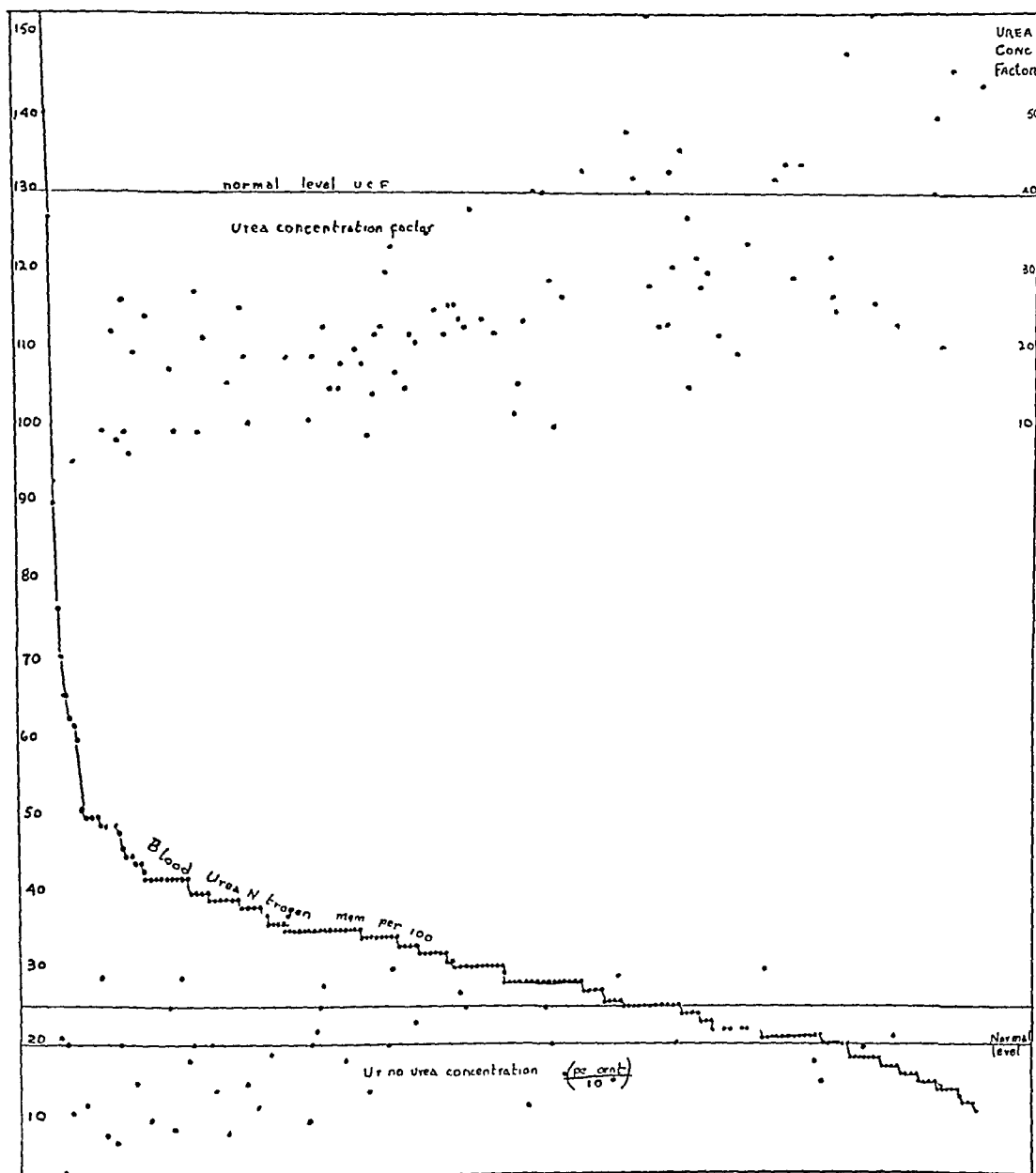


Chart 1—Blood urea nitrogen and urea concentration factor as determined in 200 normal cases

however, the kidneys have an enormous amount of reserve capacity, disturbances in function will not be noted until only the minimum essential functioning tissue is left. The most sensitive test should be the one which shows a functional disturbance in the greatest number of such cases. It will be noted in Table 2 that the urea concentration

In order to have a more accurate idea of normal values, a series of observations were made on persons having no albuminuria, a normal blood urea nitrogen and clinically being normal, with the exception of mild surgical lesions, lacerated hands, preoperative hernias, etc. The following routine was adopted and strictly adhered to. All subjects were hospital ward cases and could thus be kept from factors influencing the test, food, fluids, etc. No food or fluids of any kind were allowed after 6 p. m., the day before the test, and the usual procedure followed as described with the urea concentration test above. A specimen of blood was also obtained prior to the administration of the urea.

The data thus obtained were (a) blood urea before the administration of urea, (b) blood urea two hours after administration of urea, (c) urine urea concentration one hour and two hours after giving urea, and (d) urea concentration factor  $\frac{\text{Mg urine urea per 100 c.c.}}{\text{Mg blood urea per 100 c.c.}}$

TABLE 1—*Normal Data*

		Mg Per 100 C c
Blood urea nitrogen (before giving urea)	Lowest	13
	Highest	21
	Mean of all values	18
Blood urea nitrogen (after giving urea)	Lowest (increase)	2
	Highest (increase)	20
	Mean of all values	9
Urea concentration (urine) after 15 g. urea		Per Cent
	Mean of all values	2.38
	Lowest	1.64
	Highest	3.86
Urea concentration factor	Lowest	29.6
	Highest	81.8
	Mean of all values	41.1

TABLE 2—*Results of Two Hundred Cases*

	Number of Cases	Per Cent of Total
Subnormal urea concentration factor	167	83.5
Increased blood urea nitrogen	140	70.0
Subnormal urine urea concentration	113	56.5
Types of Cases		
Normal blood urea (upper limit) and normal urine urea concentration (lower limit)	22	11.0
Normal blood urea and low urine urea concentration	26	13.0
Increased blood urea and normal urea concentration	65	32.5
Increased blood urea and diminished urine urea concentration	87	43.5
Normal urea concentration factor	33	16.5
Normal urea concentration factor in the presence of a normal blood urea or urine urea concentration	6	3.0

All blood urea values are recorded in terms of mg. urea nitrogen. Comparing our normal data as shown in the Table 1 with those of Harrison's quoted above, it will be noted that the urea concentration factor was greater, both in the lowest and highest findings, the maximum blood urea concentration following the ingestion of urea was less, and the increase in the blood urea after ingestion or urea over that found before ingestion was also less. From a consideration of these data and the clinical picture of the subjects, it is apparent that these data and clinical pictures of the subjects more closely approximate normal values. The fact that these data were obtained half an hour earlier than those of Harrison's after giving the urea can have little bearing on the results, since both Harrison's and these data show that in the majority of cases the maximum urine urea concentration is reached at the end of the second hour. It is therefore reasonable to assume that at this period the blood will be found to have the maximum amount of urea, since the amount of urea in the blood governs the rate of excretion.

TABLE 3—Results of Two Hundred Cases—(Continued)

Record No	Blood		Urine		Urea Concentration Factor	Record No	Blood		Urine		Urea Concentration Factor
	Urea Nitrogen, Mg per 100 C c		Urea Concentration, per Cent				Urea Nitrogen, Mg per 100 C c		Urea Concentration, per Cent		
	After Urea	Before Urea	First Hour	Second Hour			Before Urea	After Urea	First Hour	Second Hour	
958	26	36	1 64	1 98	25 7	2187	22	36	1 20	1 00	13 2
868	26	34	1 20	1 68	23 2	2041	22	32	2 46	2 18	31 6
29	26	41	1 26	1 32	15 6	2030	22	29	1 72	1 70	27 6
960	25	31	1 76	1 92	28 6	1961	22	34	2 14	2 20	30 2
1599	22	30	1 18	2 10	30 2	1662	18	28	1 56	1 48	24 6
1581	22	26	0 84	1 20	21 7	11-1	18	26	1 80	1 86	33 6
1030	21	32	2 86	3 00	43 2	2168	17	30	2 20	2 40	37 3
842	21	29	2 04	2 40	38 6	1970	17	22	1 32	1 49	31 6
771	21	28	2 08	1 98	33 0	1960	17	29	1 68	1 70	27 4
261	21	36	1 32	1 44	18 6	9-1	17	28	1 63	1 49	24 8
63	21	34	3 00	2 76	37 6	98	16	24		3 00	58 4
2589	21	29	0 96	1 08	17 6	2267	16	22	2 04	2 22	47 2
2514	21	38	3 00		36 7	1548	16	20	1 80	1 90	44 1
2180	21	33	2 12	2 40	33 7	8-1	16	23	3 00	3 00	63 0
2164	21	27	3 00	2 70	46 2	226	15	16	1 26	1 48	26 6
2108	21	35	1 44	1 68	22 6	2417	15	18	2 08	1 96	50 9
1853	21	24	0 66	1 10	21 7	1550	15	19	1 30	1 90	46 7
1823	21	29	1 02	1 34	21 7	1535	15	24	0 84	1 20	23 3
2511	20	34	3 00		41 7	1536	14	23	1 98	1 90	37 4
2091	20	36	1 56	1 56	20 2	5-1	14	19	1 92	1 86	45 8
1186	20	32	1 58	1 56	22 4	30	14	24	1 68	1 85	36 6
1714	20	29	2 04	2 76	44 5	2060	14	22	2 31	1 59	33 6
1648	20	27	2 22	2 06	35 7	1571	14	23	1 80	1 96	39 6
1607	29	30	1 56	1 83	28 6	3-1	13	19	2 28	2 04	50 0
2041	19	28	1 20	2 04	34 0	1714	12	22	2 04	0 96	20 4
1549	19	32	2 80	3 00	43 6	1552	12	18	2 52	2 16	56 1
2046	18	29	1 50	1 70	27 4	2-1	12	24	2 13	1 76	34 3
1969	18	26	0 74	1 00	17 6	1551	11	20		1 20	28 0
1964	18	25	2 00	2 10	39 6	1-1	11	17		2 02	55 6

factor was the most sensitive test, the blood urea the next and the urine urea concentration the least. If one considers the factors which influence the results of the urea concentration factor, the fallacy of depending on the blood urea alone or on the urine urea concentration alone is obvious. The earliest evidence of impairment in renal efficiency may be but a slight inability to concentrate. During the day the kidneys may, however, completely remove all the waste products formed, and therefore the blood urea concentration will be normal. Since the amount of urea in the blood governs the rate of urine urea excretion, a high blood urea may at times be associated with a normal or nearly normal urine urea concentration. Therefore the fallacy of depending on the urine urea concentration alone also becomes obvious. In either of these instances, as shown in Table 3, the urea concentration factor shows impairment. This test failed in only six cases out of the total 200 studied.

In fifty other cases previously studied the necessary data for the determination of the urea concentration factor were obtained but were not then considered from this point of view. An added interest lies in the results obtained in these cases in that in all of them the phenol-sulphonephthalein test was made. It is generally recognized that remarkable fluctuations may at times occur in the dye excreted, leading

TABLE 3—Results of Two Hundred Cases

Record No	Blood		Urine		Urea Concentration Factor	Record No	Blood		Urine		Urea Concentration Factor
	Urea Nitrogen, Mg per 100 C c		Urea Concentration, per Cent				Urea Nitrogen, Mg per 100 C c		Urea Concentration, per Cent		
	After Urea	Before Urea	First Hour	Second Hour			Before Urea	After Urea	First Hour	Second Hour	
381	162	154		0.84	2.4	504	42	53	2.04	2.22	19.5
1763-1	146	140	1.20	0.84	2.6	1086	42	49	1.47	1.87	17.7
1631	140	127	0.76	0.80	2.6	1083	42	50	1.02	1.02	9.5
122	95	90	1.98	2.10	10.3	45	42	46	0.96	1.20	
1814	79	77	0.43	0.36	2.1	472	42	49	2.04	1.92	12.1
1149	86	71	1.41	2.00	10.8	366	42	43		1.53	18.3
314	69	66	0.26	1.14	7.6	331	42	44	2.40	2.56	16.6
279	72	63	0.78	0.86	5.5	456	42	48	1.14	0.96	27.2
1027	70	62	0.72	0.78	5.2	1296	42	46	1.44	2.16	9.3
1916-1	76	60	1.78	1.80	11.1	136	40	50	3.00	2.90	21.9
1024	59	51	1.44	1.38	10.9	471	40	48	2.40	2.40	27.1
649	56	56	0.80	0.96	8.0	24	40	47	1.68	1.85	23.3
379	60	50		1.26	9.6	799	40	53	1.80	2.00	18.3
337	54	50	0.90	0.96	8.3	312	39	46	1.80	1.56	17.6
2011-1	55	49	2.76	2.91	22.8	2117	39	43	1.98	1.68	15.8
1812	54	49	0.93	0.88	7.6	2247	39	54	3.00	2.90	18.2
691	53	49	2.76	3.00	26.5	1381	39	49	1.70	2.04	25.1
904	61	49	0.96	1.28	9.6	1085	39	57	1.64	1.41	19.4
1726	53	48	1.64	0.72	6.3	1084	39	42	2.88	2.60	11.5
515	49	46	2.28	2.08	19.6	315	38	47	1.86	1.98	29.0
716	54	45	2.94	3.00	25.8	688	38	46	2.40	2.18	19.7
134	55	45	2.40	2.88	24.4	967	38	43	1.11	0.80	22.1
2354	49	44	1.20		11.4	551	38	48	1.32	1.63	8.6
26	47	44	1.50	1.56	15.5	1056	37	43	1.82	1.59	16.3
2288	52	43	1.80	1.86	16.7	311	37	49	1.32	1.20	17.2
											11.4
1739	36	46	1.62	1.83	18.6	1582	34	40	1.50	1.30	15.1
779	36	43	1.54	1.54	18.8	549	34	37	1.82	1.74	21.8
2661	36	42	2.10	1.68	18.7	522	34	39	1.76	1.80	21.5
540	36	40	2.64	2.82	32.9	1161	33	40	1.74	1.51	17.6
1094	35	43	1.20	1.20	13.0	725	33	42	2.53	2.38	26.5
1112	35	47	1.16	1.12	11.0	500	33	40	3.00	3.00	35.0
1310	35	42	1.46	1.71	19.0	1874	33	36	2.10	2.16	28.0
968	35	50	1.72	1.87	17.4	1738	32	35	1.92	1.86	24.8
894	35	46	2.20	2.28	23.1	1775	32	39	1.40	1.40	16.7
867	35	46	1.26	1.50	15.2	2061	32	37	1.70	2.10	20.6
764	35	43	2.16	2.40	26.0	1129	32	36	2.00	2.80	26.5
163	35	47	1.44	1.50	14.9	959	32	34	1.88	1.92	26.4
627	35	43	1.50	1.63	18.2	2645	32	42	1.92	2.16	24.0
1572	35	47	0.60	2.16	16.0	1536	31	40	1.89	2.04	23.5
1780	35	39	0.66	1.70	20.2	2193	31	37	3.00	3.00	37.9
2240	35	41	1.62	1.58	18.0	1875	30	34	0.66	1.44	19.8
434	35	40	2.40	0.74	8.6	1360	30	40	1.84	2.75	32.1
581	35	36	0.96	1.08	14.0	1207	30	36	1.92	1.88	24.4
2651	35	42	1.98	2.01	22.3	626	30	38	2.24	2.60	31.8
2560	35	44	2.20	2.20	23.3	2526	30	32	1.92	2.28	35.3
1374	34	40	0.83	2.50	29.6	228	30	41	2.34	2.38	27.1
1278	34	39	3.00	2.80	33.5	25	30	40	1.80	1.92	22.4
1113	34	46	2.01	3.00	30.4	523	30	36	2.10	2.20	28.6
648	34	42	1.68	1.56	17.3	211	30	33	1.56	1.80	25.4
2353	34	41	2.00	2.40	27.3	674	30	32	1.65	1.82	26.5
2102	29	36		0.96	12.4	1206	25	32	1.50	1.96	29.7
999	28	38	1.20	1.29	15.8	1280	25	27	1.59	2.13	36.8
1174	28	30	1.92	1.56	24.4	1358	25	26	1.42	2.10	48.5
1246	28	34	1.59	2.17	30.7	960	25	35	1.76	1.92	26.2
1270	28	35	3.00		40.0	908	25	36	2.04	2.10	42.5
1401	28	36	1.40	2.70	34.5	870	25	30	1.56	1.68	28.5
1128	28	30	2.42	2.60	40.5	671	25	33	3.00	3.00	15.8
1125	28	33	1.44	1.88	26.3	613	25	37	2.16	2.16	25.7
843	28	31	1.80	1.92	28.6	2273	25	32	1.56	1.08	63.4
582	28	40	0.78	0.84	9.8	1774	25	40	1.70	2.20	40.0
435	28	42	2.82	3.00	33.4	1163	18	22	3.00	3.00	28.0
348	28	39	2.52	2.28	27.3	1307	24	28	2.18	2.40	29.0
28	28	33	1.50	1.53	21.6	2320	24	36	1.80	2.20	22.6
2413	28	29	1.76	1.98	31.0	1815	24	30	0.99	1.89	42.5
2351	28	32	2.64	3.00	43.5	1596	24	33	0.37	1.50	22.6
1583	28	36	0.84	1.20	15.5	1057	23	33	2.58	3.00	43.2
1123	27	32	2.54	3.00	43.5	555	23	30	2.16	1.86	30.7
31	27	40	1.22	1.20	14.6	2037	23	26	1.90	2.04	36.2
2194	27	39	1.50	2.20	26.3	1187	22	30	3.00		46.2
1889	27	37	2.25	2.50	31.6	873	22	27	0.90	0.96	16.6
961	26	38	1.88	2.04	25.6	2481	22	29	2.34	2.36	38.2

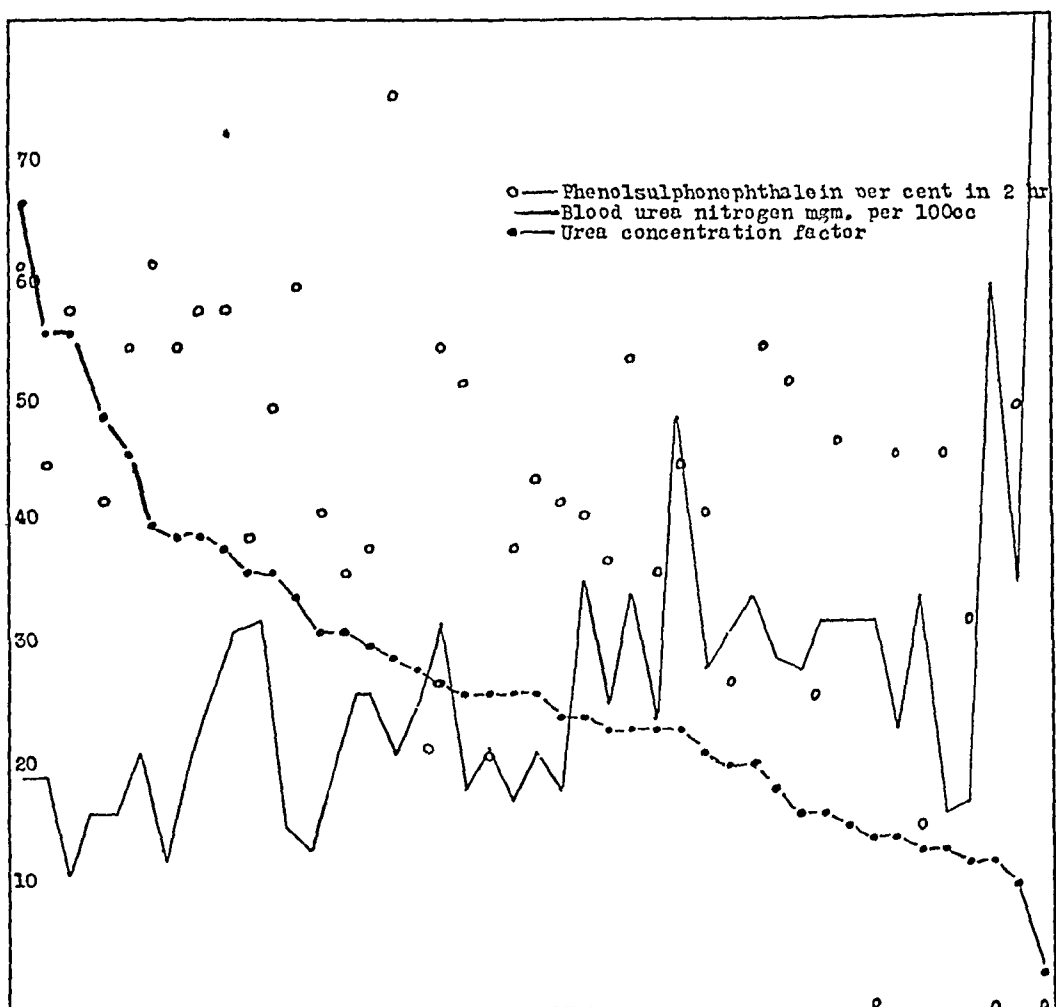


Chart 4—Urea concentration factor from normal to low values

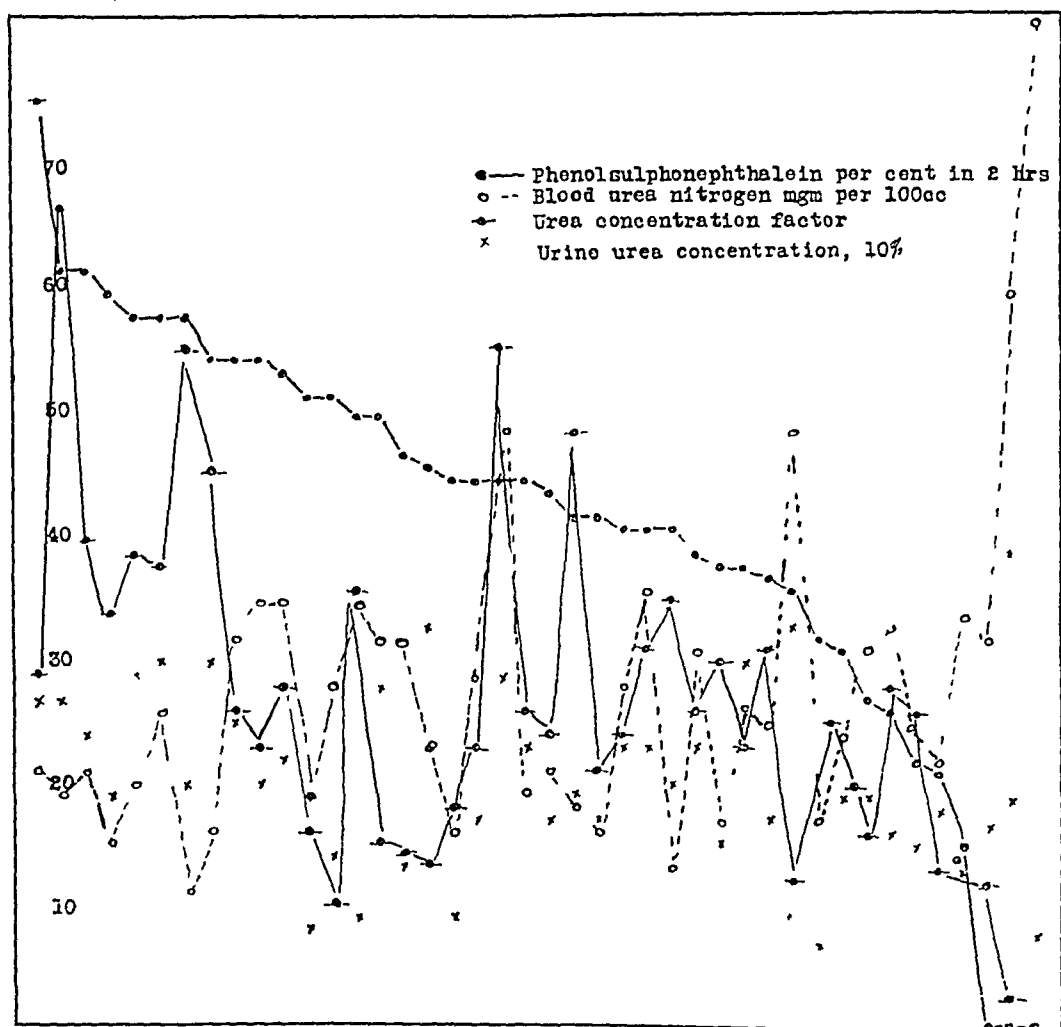


Chart 5—Phenolsulphonephthalein excretion from normal to low

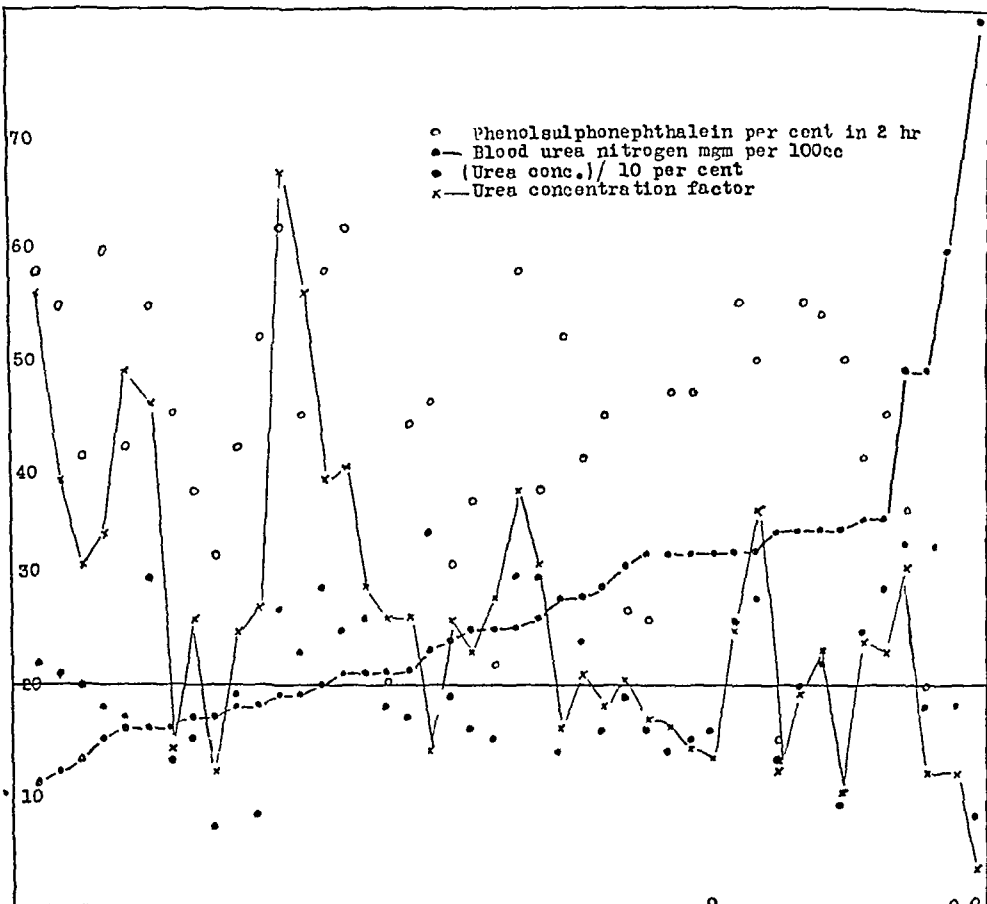


Chart 2—Blood urea concentration from normal to high values

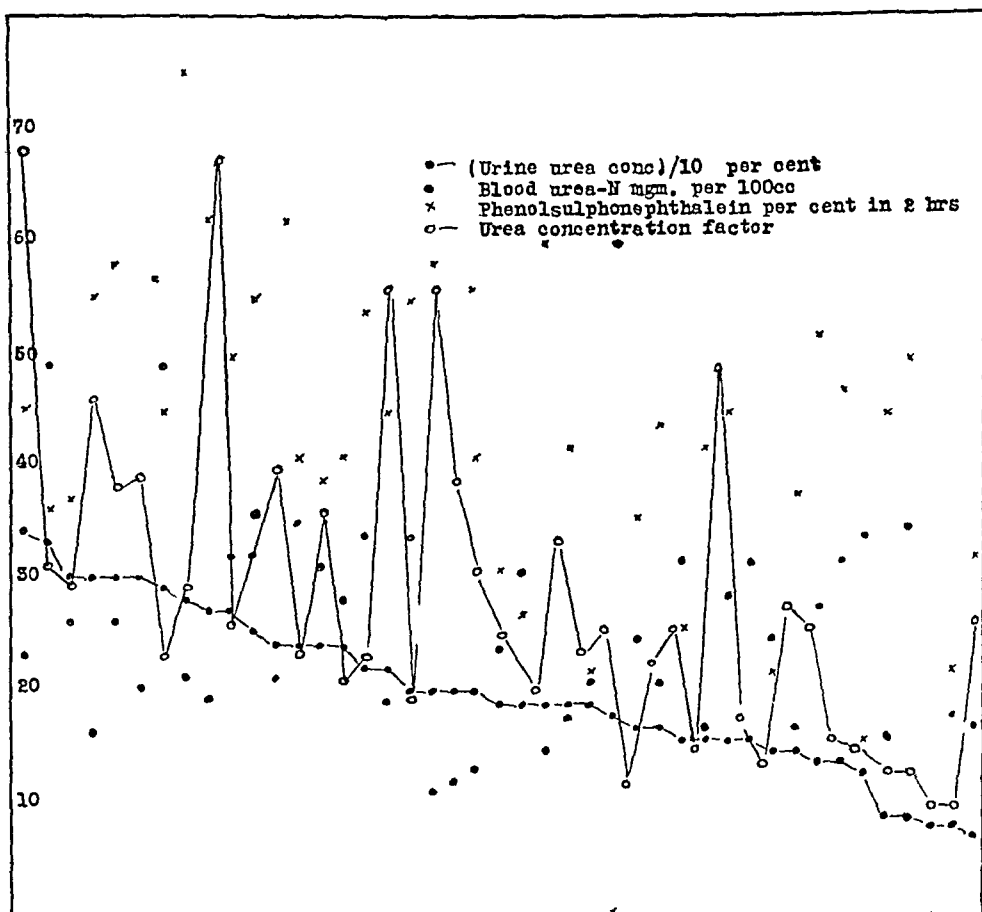


Chart 3—Urine urea concentration variations from normal to low values

# TREATMENT BY SPLENECTOMY OF ESSENTIAL THROMBOCYTOPENIA (PURPURA HEMORRHAGICA)

N E BRILL, M D, AND N ROSENTHAL, M D

NEW YORK

The rôle of the blood platelets in hemophilia and purpura hemorrhagica, which comprise the hemorrhagic diseases, is of paramount importance. Hemophilia is the result of some qualitative change in the blood platelets (Fonio,<sup>1</sup> Minot and Lee<sup>2</sup>) resulting in defective coagulation of the blood. Purpura hemorrhagica is accompanied by a qualitative change and by a greatly diminished number of blood platelets, also by some change in the capillary activity resulting in a hemorrhagic tendency. This constant diminution of the platelets without any known cause (Denys,<sup>3</sup> Hayem<sup>4</sup>) has given rise to the better modern name of essential thrombopenia (Frank<sup>5</sup>) or better still, thrombocytopenia (Eppinger<sup>6</sup>). Essential thrombocytopenia is a distinct clinical entity and is characterized by the following main features:

- 1 Diminution of the blood platelets. The average number of blood platelets in normal blood is 250,000. The platelets vary from none to 100,000 in this disease, at times the number may reach the normal figure. Hemorrhagic manifestations come into evidence when they fall below 60,000.

- 2 Preservation of normal coagulation time of the venous blood.

- 3 Prolongation of bleeding time (Duke<sup>7</sup>). Puncture of the lobe of the ear is followed by some oozing of blood for from one to three minutes normally. In thrombocytopenia this is prolonged usually from ten minutes to hours.

- 4 Positive capillary resistance test (Hess<sup>8</sup>). A tourniquet applied to the arm sufficient to prevent the return circulation without obliterating the pulse is followed by a shower of petechiae.

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\* Paper read at the meeting of the Association of American Physicians held at Atlantic City, May 1, 1923.

\* From the First Medical Division, Mount Sinai Hospital, New York.

1 Fonio. *Col -Bl f Schweiz Aerzte* **45** 1505, 1915.

2 Minot, G R, and Lee, R I. *Blood Platelets in Hemophilia*, *Arch Int Med* **18** 474 (Oct) 1916.

3 Denys, J. *La Cellule* **3** 445, 1887.

4 Hayem, G. *Presse med* **3** 233, 1895.

5 Frank, E. *Berl klin Wchnschr* **52** 454 and 490, 1915.

6 Eppinger, H. *Die hepatolienalen Erkrankungen in Enzyklopadie der Klinischen Medizin*, 1920.

7 Duke, W W. *The Pathogenesis of Purpura Hemorrhagica with Especial Reference to the Part Played by Blood Platelets*, *Arch Int Med* **10** 445 (Nov) 1912.

8 Hess, A F. *Hemophilia*, *Arch Int Med* **17** 203, (Feb) 1916.



to results inconsistent with the clinical picture. The comparative results of all the different tests used in these cases are recorded graphically. For detailed data of these cases the reader is referred to the original article.<sup>4</sup> In Chart 2 the blood urea concentration findings are recorded from normal to abnormal values consecutively. The same is done in Chart 3 with the urine urea concentration, in Chart 4 with the urea concentration factor and in Chart 5 with the phenolsulphonephthalein excretion. In each instance all other data obtained in the same case are recorded. It will be noted that the results of the urea concentration factor, approximate the blood and urine data, showing either improvement or a decrease in function. The phenolsulphonephthalein results show no such relation with either blood urea, urine urea concentration, or the urea concentration factor.

#### CONCLUSIONS

In renal lesions associated with azotemia or any other evidence of impairment in excretion of nitrogenous substance, the urea concentration factor appears to be a more sensitive test for renal efficiency than the other tests now in use. A distinct advantage of this test is that a combination of both blood and urine studies must be made in each case.

100,000 and occasionally as low as 50. We have never observed their complete disappearance when they are counted directly in undiluted citrated plasma. In the intermittent type of thrombocytopenia the hemorrhagic tendency becomes evident when the number of blood platelets falls below 10,000, or less. Clot retraction is usually absent even when the blood platelets are as high as 80,000. There is a certain parallelism between the bleeding time, capillary resistance test and the number of blood platelets.

Concerning the cause of the thrombocytopenia there are two main theories. (1) Diminished production of the blood platelets as a result of some toxic or inhibitory action of the spleen on the megakaryocytes of the bone marrow which, according to Wright,<sup>14</sup> are the mother cells of the blood platelets. This theory proposed by Frank<sup>5</sup> led to the treatment of chronic thrombocytopenia by means of splenectomy. (2) In such cases Minot<sup>15</sup> found no diminution of the megakaryocytes in the bone marrow. Kaznelson frequently noticed enlargement of the spleen and came to the conclusion that an increased function on the part of this organ in the destruction of blood platelets was responsible for their diminution in the blood. Kaznelson<sup>16</sup> was the first to apply this knowledge and have a splenectomy performed in a case of chronic thrombocytopenia. The spleen of this case showed the presence of numerous large blood platelets. He suggested the name thrombolytic purpura for the condition. We shall discuss the validity of these theories later.

#### SPLENECTOMY FOR ESSENTIAL THROMBOCYTOPENIA

The exceptionally good results from splenectomy reported by Kaznelson<sup>17</sup> soon made the procedure the method of choice as a remedial or life saving measure in this disease when all other therapy has failed. So far seventeen cases of essential thrombocytopenia (including two reported in this paper) have been treated by splenectomy (Table 1).

The postoperative course in all the successful cases was about the same. The following points are noteworthy.

1 Blood platelet crisis. The increase varied from 25,000 to 1,500,000.

2 Immediate cessation of the hemorrhagic tendency. In a few cases the tendency reoccurred, but not as severely as formerly.

14 Wright, J. H. *Boston M. & S. J.* **154** 643, 1906.

15 Minot, G. R. *Diminished Blood Platelets and Marrow Insufficiency*, *Arch. Int. Med.* **19** 1071 (June) 1917.

16 Kaznelson, P. *Wien klin. Wchnschr.* **29** 1451, 1916.

17 Kaznelson, P. *Ztschr. f. klin. Med.* **87** 133, 1919.

5 Failure of clot retraction (Hayem<sup>9</sup>) Clot retraction does not occur before splenectomy in this disease even when the blood platelets increase to 80,000 In a few obscure cases the blood platelets may be normal in number without clot retraction but accompanied by the other characteristics of essential thrombocytopenia, such as a prolonged bleeding time and positive capillary resistance test Glanzmann<sup>10</sup> has attributed this to some defect of the blood platelets and has called this condition thrombasthenia

The clinical manifestations of thrombocytopenia are

1 Acute or chronic thrombocytopenia A patient with an acute case may get well, run a short fatal course or his case may become chronic The chronic condition as a rule appears in young persons, usually girls

2 Apparently spontaneous hemorrhages into the skin and from mucous membranes, which may be continuous or intermittent

3 Excessive hemorrhage from slight trauma The outcome is usually weakness and physical incapacity, owing to a severe grade of anemia following the intermittent attacks of hemorrhage Death not infrequently occurs from exsanguination

#### PATHOGENESIS

Capillary hemorrhage is normally stopped by the production of a small blood platelet thrombus and by the inherent contractility of the vessels The thrombus results from the adhesion and rapid agglutination of the blood platelets in the opening of the vessel from which the blood is oozing The thrombus acts like a dam and prevents further bleeding

One of the normal functions of the circulating blood platelets is to prevent the diapedeses of the red blood cells between the endothelial cells of the capillaries (Frank<sup>11</sup>) There is also some proof that the blood platelets participate in the control of vascular contractility (O'Connor,<sup>12</sup> Janeway<sup>13</sup>), this contractility also reenforces the protective mechanism against capillary hemorrhage Any disturbance in the production or of the function of the blood platelets brings about a bleeding tendency due to the subsequent effect on the activity of the capillaries The slightest trauma to the body then becomes evident by the appearance of hemorrhages, often uncontrollable An examination of the blood during such a period in a case of essential thrombocytopenia will reveal the marked diminution of the blood platelets, usually below

9 Hayem, G Compt rend Acad d sc **123** 894, 1896

10 Glansmann Jahrb f Kinderheilk **88** 1 and 113, 1918

11 Frank, E Eulenburgs Real-Enzyklopadie, dritter Ergänzungsband Ergebnisse der gesamten Medizin, Berlin **3** 171, 1922

12 O'Connor, J M Munchen med Wchnschr **58** 1439, 1911

13 Janeway, T C, Richardson, H B, and Park, E A Experiments on the Vasoconstrictor Action of Blood Serum, Arch Int Med **21** 565 (May) 1918

*Physical Examination*—The patient was fairly well nourished, well developed and acutely ill. There was marked pallor of the face. She vomited dark red blood repeatedly. She had pyorrhea. The gums were somewhat spongy but they were not bleeding. Blood clots were seen in the pharynx. She had bilateral adenopathy. There was a loud blowing systolic murmur at the apex of the heart not transmitted. The liver was not palpable. The spleen was felt 1 cm below the costal margin. There was slight pretibial edema. There were old scars and pigmented areas. There were widely distributed hemorrhagic areas varying in size from a petechia to a large ecchymosis. These areas were most marked on the legs and were confluent.

*Treatment and Course*—On Oct 26, 1922, direct transfusion (Unger method) of 600 cc was performed. There was no bleeding for five days following this transfusion. A distinct increase in the size of the spleen was noted, 3 cm below the costal margin. Oct 30, 1922, blood examination revealed hemoglobin, 38 per cent (Kuttner), red cells, 2,272,000, white cells, 6,800, platelets, 6,400 differential count, 300 cells counted polymorphonuclear neutrophils, 54.3 per cent, polymorphonuclear eosinophils, 16 per cent, polymorphonuclear basophils, 2 per cent myelocytes, neutrophilic, 13 per cent, lymphocytes, 25.6 per cent plasma cells, 2 per cent, monocytes, 13 per cent, and normoblasts 1 per 300 white cells. The coagulation time of the blood was ten minutes (test tube). Bleeding was profuse at the end of ten minutes. The capillary resistance test was positive within two minutes. There was no clot retraction.

*Diagnosis* Secondary anemia, essential thrombocytopenia.

Nov 2 to Nov 5, 1922. There was repeated vomiting of old and fresh blood.

On examination of the throat, bright red blood was seen issuing from the nasopharynx.

Nov 5, 1922. The hemoglobin content was 27 per cent. Direct transfusion (Unger method), 500 cc, was performed.

Nov 9, 1922. Slight epistaxis. The patient vomited blood once.

Nov 13, to Nov 15, 1922. Slight epistaxis and vomiting blood. On November 15, 20 cc of horse serum was given intramuscularly without effect.

Nov 16, 1922. The hemoglobin content was 32 per cent. Direct transfusion (Unger method), 750 cc, was performed. There was no reaction.

Nov 19, 1922. The hemoglobin content was 43 per cent. Vomiting blood again occurred.

Nov 20 to Nov 25, 1922. During this period the patient vomited blood repeatedly. During the later hemorrhages the pulse was so rapid that it was almost impossible to count. Otherwise the pulse varied from 120 to 140. There was marked pallor. The eyes were large and staring at times. The patient was very restless.

Nov 26, 1922. Direct transfusion (Unger method), 500 cc, was performed.

Nov 27, 1922. The hemoglobin content was 35 per cent. The general condition was poor, the pallor still marked, expression anxious. There was slight epistaxis. The patient vomited once. Most of the veins of the forearms were tender and cordlike, evidently due to intravascular clotting, making the transfusions difficult.

It was decided that splenectomy would be tried after the next transfusion, which was to be given to improve the patient's general condition.

Dec 1, 1922. Direct transfusion (Unger method), 500 cc, was performed. The transfusion had to be stopped at this point because the patient complained of severe precordial pain.

Dec 2, 1922. The hemoglobin content was 43 per cent. A splenectomy was performed by Dr. A. A. Berg. A greatly enlarged spleen was delivered through a subcostal incision. The wound bled considerably. As soon as the pedicle was clamped all bleeding stopped. There was some oozing from the nose throughout the anesthesia, this also stopped as soon as the spleen was removed. A direct transfusion of 800 cc was given immediately after the operation. The postoperative recovery was uneventful. The wound healed by primary union.

- 3 Later return of the blood platelets to their previous low level  
This took place from a few days to a few weeks after the splenectomy
- 4 Increase of the hemoglobin and the red blood cells
- 5 Apparent cure of the condition

The remarkable results reported from splenectomy led us to undertake this procedure in two cases of essential thrombocytopenia in which all known methods of treatment, especially transfusion, had failed. Both patients were in a serious condition and were almost moribund. Splenectomy brought about immediate improvement and apparent ultimate cure and undoubtedly acted at the time of operation as a life-saving measure.

TABLE 1—*Patients Treated by Splenectomy for Essential Thrombocytopenia*

Case	Date	Author	Result
1	1916	Kaznelson Wien Klin Wehnschr 29 1451, 1916, Ztschr f klin Med 87 133, 1919	Well
2	1916	Kaznelson Wien Klin Wehnschr 29 1451, 1916, Ztschr f klin Med 87 133 1919	Well
3	1916	Kaznelson Wien Klin Wehnschr 29 1451, 1916, Ztschr f klin Med 87 133, 1919	Greatly improved
4	1917	Benecke Therapie der Gegenwart 19 418, 1917	Well
5	1917	Schmidt Wien Klin Wehnschr 30 959 1917	Well
5	1917	Schmidt Wien Klin Wehnschr 30 959, 1917	Greatly improved
7	1919	Minkowski Med Klin 15 1243, 1919	Greatly improved
8	1920	Ehrenberg Monatschr f Geburtsh u Gynak 31 99, 1920	Well
9	1921	Eylenburg Folia Hemat 26 176, 1921	Well
10	1921	Kaznelson Med Klin 17 974, 1921	Died
11	1921	Kaznelson Med Klin 17 974 1921	Well
12	1921	Minot Med Klin 17 974, 1921	Well
13	1922	Cori Ztschr f klin Med 94 356, 1922	Well
14	1922	Steinbrinck Ztschr f klin Med 94 447, 1922	Greatly improved
15	1923	Bowen Bull Buffalo Gen Hosp 1 2, 1923	Well

# REPORT OF CASES

CASE 1—*R G, chronic essential thrombocytopenia (purpura hemorrhagica), splenectomy, recovery*

*History*—A girl, aged 19, was admitted to the first medical service, Mount Sinai Hospital, on Oct 26, 1922, complaining of uncontrollable bleeding from the nose, mouth and stomach. The family history and past history were negative. There were no bleeders in the family. The patient was perfectly well until she was 5 years of age, when she had an attack of "kidney trouble" (bloody urine and generalized edema). This was followed a few weeks later by an uncontrollable nasal hemorrhage, for which the child had to be taken to a hospital, where she remained for five weeks. Since then, about once each year, the patient had had an attack of severe bleeding from the nose and mouth and vomiting of blood. During the attacks she became weak and pale. The bleeding continued at varying intervals from one to five days, occasionally for a longer period. In the interval between attacks the patient usually felt quite well. However, she always noticed black and blue spots on her skin, these occurred after the slightest trauma. The menses during an attack were usually repressed. Recently the periods had been greatly prolonged.

The present attack began three days before admission after the patient had apparently been well for two years. There had been bleeding at intervals from the nose and mouth. Some of the blood coming down from the back of the nose was swallowed and then vomited.

Eight transfusions had been given within the past eight years without producing any lasting effect.

Blood Changes Following Splenectomy (Chart 1, Table 2) (a) The two transfusions—500 cc given the day before the operation and 800 cc given immediately after the operation—raised the hemoglobin to 70 per cent and the red cells to 4,352,000. The following month the hemoglobin fluctuated between 60 and 80 and then rose to 90 per cent. The red cells also followed the high percentage and later rose to 5,864,000. Four months later the hemoglobin again fell to 80 per cent, but the red cells remained over five and one-half million.

(b) The leukocytes increased to 56,000 but gradually assumed their normal number (5,600 to 7,000), and later fluctuated between 8,000 to 28,000. After the postoperative polynucleosis there followed a persistent monocytosis.

(c) The blood platelets showed the usual behavior as in other splenectomized cases of thrombocytopenia. Six hours after the operation 95,000 platelets were present. The following day they rose to 225,000 and again rose on the second

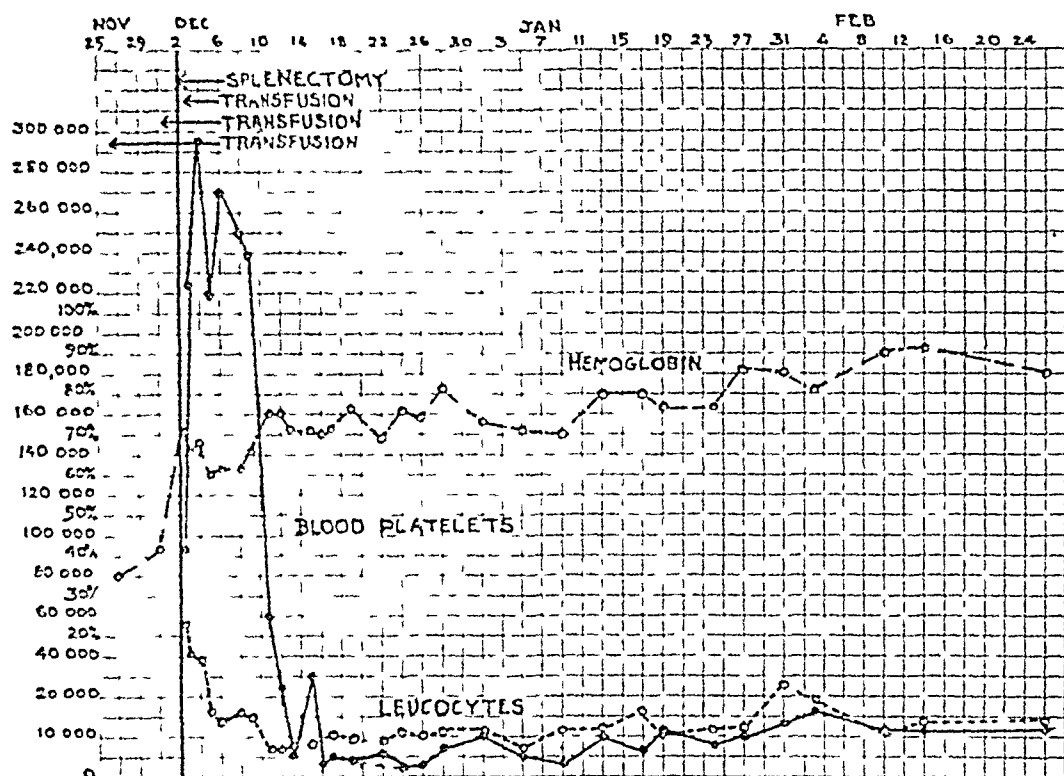


Chart 1 (Case 1)—Variations of the hemoglobin, leukocytes and blood platelets following splenectomy

day after operation to 295,000. Then within a week the platelets dropped to 5,000. After this the bleeding time was usually normal. Occasionally it was prolonged. The blood platelets were distinctly larger than normal ones.

(d) The capillary resistance test was usually negative. On one occasion a few petechiae appeared at the bend of the elbow.

(e) Slight clot retraction was present the first month. During the second month there was no clot retraction. Clot retraction appeared again the third month, but this was somewhat less than normal. Clot retraction was present at a recent examination (April 24, 1923).

*Summary of Case*—The patient had an essential thrombocytopenia (purpura hemorrhagica) of fourteen years' duration with chronic intermittent course. The patient became exsanguinated several times and received transfusions as many times, with only temporary success. All agents known to stop hemorrhage

Summary of report by Dr F S Mandlebaum The macroscopic specimen consisted of a large spleen weighing 1,400 gm and measuring 23 by 13 by 6.5 cm The surface was smooth with occasional indentation There were few adhesions on the mesial aspect The vessels were patent and not sclerotic The spleen felt elastic and cut easily The cut surface showed the presence of numerous large follicles Pulp was present in a normal amount The sinuses were not dilated or sclerosed Microscopically the spleen showed myeloid metaplasia and hyperthrophy of the malpighian bodies There were no blood platelets or thrombi

On Dec 2, 1922, six hours after the operation, crops of fresh petechiae appeared over the upper part of the left side of the chest and left cheek All

TABLE 2—R G, Case 1, Blood Examinations Following Splenectomy, Dec 2, 1922

	Hemo- globin, Per cent age	Red Blood Cells	White Blood Cells	Plate lets	Poly- morpho- nuclears, Per- cent- age	Lym- pho- cytes, Per- cent- age	Mono- cytes, Per- cent- age	Coag- ulation Time, Min	Bleed- ing Time, Min	Capillary Resis- tance Test	Clot Retraction
After 6 hours*	70	4,352,000	56,000	95,000	97.0	0.3	2.3				
12/ 3/22	66	4,141,000	40,000	225,000	93.3	2.0	4.6		1½		
12/ 4/22	68	4,064,000	39,200	295,000	87.6	3.0	9.3		2		
12/ 5/22	60	3,872,000	16,000	220,000	73.6	13.0	12.6		1		
12/ 6/22	62	3,932,000	14,400	270,000	86.0	8.6	5.3		2		
12/ 8/22	63	3,880,000	15,800	145,000	85.0	8.0	5.0		1½		
12/ 9/22	66	4,160,000	15,000	240,000	74.0	13.6	8.6		2	Negative	
12/11/22	75	4,544,000	7,000	60,000	63.0	18.3	15.3		4		
12/12/22	75	4,480,000	7,000	25,000	46.6	31.0	17.0		3		
12/13/22	72	4,520,000	6,800	5,000	60.0	24.0	13.3		8		
12/15/22	71	4,488,000	8,900	30,000	50.6	24.3	20.3		2	Negative	
12/16/22	70	4,960,000	10,000	3,000	66.6	14.0	18.3		5		
12/17/22	72	5,120,000	9,600	5,000	44.3	32.3	12.0		4		
12/19/22	77	4,832,000	10,600	4,800	65.3	17.6	12.0	10	3	Negative	Very slight
12/22/22	68	4,480,000	9,000	6,000	62.3	26.6	7.3		2		
12/24/22	76	4,736,000	12,200	3,000	56.6	28.0	12.0		2		
12/26/22	71	4,800,000	10,200	4,000	61.0	28.3	9.0		2		
12/28/22	82	5,200,000	12,400	7,500	53.3	32.0	12.3		1½		
1/ 1/23	74	4,576,000	10,200	10,000	59.0	30.3	9.6		2		
1/ 5/23	71	4,512,000	7,800	5,000	31.6	47.0	10.6		½		
1/ 9/23	70	4,120,000	12,000	4,000	45.3	32.6	17.6		9	Negative	
1/13/23	80	5,120,000	11,600	10,000	48.6	42.3	6.3		½		
1/17/23	80	5,632,000	16,000	6,000	54.0	36.6	9.0				
1/24/23	76	4,736,000	12,800	8,000	57.3	33.3	7.6		0		
1/27/23	87	5,376,000	13,800	10,000	52.6	36.6	10.3	11	3	Negative	None
1/31/23	87	5,440,000	28,000	14,000	51.0	39.0	19.3				
2/ 3/23	80	5,564,000	19,800	16,000	53.3	36.6	9.0				
2/10/23	90	5,864,000	11,200	12,000	54.0	38.0	6.3				
2/13/23	92	6,194,000	12,400	12,000	57.0	36.6	5.3	8	3	Slightly positive	Present
4/24/23	84	6,656,000	14,200	20,000	62.6	26.3	9.6	6	4½	Negative	Present

\* Following two transfusions

bleeding from the mucous membranes stopped The hemoglobin content rose to 70 per cent

Dec 2, 1922, to April 10, 1923 There was steady improvement The color gradually returned, the cheeks and lips were red The patient felt perfectly well There was a cessation of all hemorrhage from the nose For a short period after the splenectomy there was slight bleeding from the gums but none after that The patient vomited three times after the operation, but there was no blood in the vomitus She vomited a slight amount of blood only once later Petechiae appeared about six hours after the operation, but none had appeared since All the hemorrhagic areas disappeared Black and blue marks did not appear as formerly Recently the patient "turned" her knee cap, but only a slight skin hemorrhage developed Before operation there was a marked urobilin reaction in the urine, after operation, a faint trace

injected intramuscularly and 10 cc injected slowly into the nose arrested the bleeding. The hemoglobin content was 30 per cent. Early in the morning (4 a m) the patient again began to bleed from the nose. The pulse was rapid, 140, later (6 30 a m), 150. The hemoglobin content was 29 per cent, platelets, 300 (plasma). Direct transfusion (Unger method), 500 cc, was performed.

Dec 18, 1922. There had been no bleeding since the transfusion was performed. There was a slight rise in temperature to 102.8 F. The hemoglobin content was 38 per cent, red cells, 2,634,000, white cells, 19,400, polymorphonuclear neutrophils, 91 per cent, lymphocytes 7 per cent, monocytes, 2 per cent, and platelets, 27,500. The bleeding time was thirteen minutes, the coagulation time, eight minutes. The capillary resistance test was negative. There was no clot retraction.

Dec 19, 1922. There was a crop of new petechiae on all extremities.

Dec 22, 1922. The patient had edema of the uvula and tonsil—traumatic.

Dec 23, 1922. The hemoglobin content was 28 per cent, red cells, 2,010,000, platelets, 24,000.

Dec 25 to Dec 29, 1922. Fresh petechiae appeared daily. The general condition was becoming worse. Pallor and weakness were marked.

Dec 29, 1922. Splenectomy was decided on for the relief of the condition.

TABLE 3—Case 2, Blood Examinations Before Splenectomy

	May 5, 1919	May 1, 1922	Nov. 26, 1922	Dec 18, 1922	Dec 30, 1922
Hemoglobin	70%	78%	17%	38%	48%*
Red cells	3,900,000	1,800,000	2,584,000	2,634,000	2,896,000
White cells	23,000	11,000	10,000	19,400	22,000
Platelets	80,000	50,000	10,000	24,000	None
Polymorphonuclear neutrophils	8%	63.5%	71.6%	91%	72.3%
Lymphocytes	1%	27.5%	15.3%	7%	14.3%
Monocytes	4%	7.5%	11.0%	2%	6.3%
Coagulation time	5 min	10 min	10 min	8 min	4 min
Bleeding time	7 min	16 min	4½ min	13 min	Profuse at end of 6 min
Capillary resistance test	Slightly positive	Slightly positive	Slightly positive	Positive	Slightly positive
Clot retraction	None	None	None	None	None

\* Day following transfusion of 500 cc whole blood.

Direct transfusion (Unger method), 450 cc, was performed. There was a severe reaction following transfusion. The patient had a chill with rise of temperature to 105 F.

Dec 30, 1922. Splenectomy was performed by Dr. E. Beer through a subcostal incision. There was profuse oozing of the wound. Continuous oozing from the nose occurred during the anesthesia.

A soft, slightly enlarged spleen with omental adhesions between the stomach and hilus was found. The adhesions were doubly divided and cut. The spleen was delivered with some difficulty. The hilus was ligated and cut, taking special care not to include the adherent stomach.

Summary of Pathologic Report by Dr. F. S. Mandlebaum. The macroscopic specimen consisted of a moderately enlarged spleen weighing 300 gm and measuring 14 by 7.5 by 3 cm. It was elastic and cut easily. Malpighian bodies were visible. Microscopic examination showed only hypertrophy. No blood platelets were found.

Immediately after the removal of the spleen, all oozing of blood stopped from the wound and nose. The same effect was noted for the bleeding time as in the previous case.

The bleeding before splenectomy was profuse at the end of six minutes, when it was stopped. The bleeding time during manipulation at the hilus was six minutes, immediately after splenectomy, three minutes, two hours after splenectomy, three minutes, eight hours after splenectomy, three minutes, and fifteen hours after splenectomy, two and one-half minutes (Tables 3 and 4).



were of no avail until splenectomy was performed, following which there was no further bleeding. The patient was discharged apparently well. The hemorrhagic tendency had stopped.

**CASE 2**—Chronic essential thrombocytopenia (purpura hemorrhagica), splenectomy, recovery

*History*—A boy, aged 15, was admitted to the first medical service on Nov 22, 1922, complaining of bleeding from the nose and vomiting of blood. The family history and past history were negative. There were no bleeders in the family. The present illness began in April, 1919, when the patient had an attack of tonsillitis followed by hemorrhages into the skin, bleeding from the gums, painful joints, vomiting and pain in the upper part of the abdomen. He also had irritability of the eyes, weakness, fever, chills and sweats. He remained in the hospital for one month. He was apparently well except for an occasional ecchymosis following some slight trauma, until May, 1922, when he received a blow on the nose. This was followed by a severe epistaxis which continued for several hours. The bleeding was stopped by means of a tampon saturated with fresh normal blood. The skin hemorrhages had become more frequent since. In July, 1922, while drinking milk, blood began to issue from the anterior and posterior nares, and soon the patient vomited blood and food. Some hemorrhagic areas again appeared on the skin and roentgen-ray therapy was applied to the splenic region, with apparently good results. His condition improved. He lived a quiet life until the day of his recent admission to the hospital, Nov 22, 1922, when he was again struck on the nose, and he had been bleeding and vomiting blood ever since.

*Physical Examination*—The patient was a well developed and fairly well nourished boy with marked pallor. He appeared to be acutely ill. There were a few petechiae in the conjunctivae of both lower lids. The teeth were in fair condition. The gums were spongy and bleeding, the tonsils large and covered with hemorrhagic spots. The heart was not enlarged. There was a systolic thrill and murmur at the apex. The spleen was not palpable, but it was large to percussion. There were numerous petechiae over the back, chest, abdomen, thighs and legs.

On Nov 26, 1922, the blood count was: hemoglobin, 45 per cent, red cells, 2,584,000, white cells, 10,000, platelets, 10,000 (plasma), polymorphonuclear neutrophils, 71.6 per cent, polymorphonuclear eosinophils, 1.6 per cent, polymorphonuclear basophils, 0.3 per cent, lymphocytes, 15.3 per cent, and monocytes, 1.1 per cent. The coagulation time of the blood was ten minutes, the bleeding time four and one-half minutes.

The tourniquet test was slightly positive. There was no clot retraction. The patient had secondary anemia, thrombocytopenia and monocytosis. The blood picture was characteristic of essential thrombocytopenia.

*Treatment and Course*—Nov 29, 1922. There were no further hemorrhages. The petechiae on the legs had disappeared. The spleen was not palpable.

Dec 2, 1922. The patient had epistaxis at intervals all day.

Dec 6, 1922. The hemoglobin content gradually fell until it was 28 per cent. The patient still bled daily from the nares. The platelets numbered 8,000.

Dec 9, 1922. The gums were spongy and bleeding. The condition was becoming worse. The bleeding from the nose had stopped.

Dec 12, 1922. Slight bleeding from the gums continued. There was marked pallor and weakness. Blood examination (Table 4) showed hemoglobin, 28 per cent, red cells, 2,204,000, and platelets, 400. The bleeding and coagulation time were normal. The capillary resistance test was negative, but there was no clot retraction.

Dec 16, 1922. The patient vomited about 7 ounces of dark clotted blood. The blood trickled down from the posterior nares.

Dec 17, 1922 at 12 50 a m. There was bleeding both from the anterior and posterior nares. Thromboplastin and epinephrin did not control bleeding. The tampon was not tolerated. Twenty cubic centimeters of unmodified blood

Feb 17, 1923 The patient was discharged well

**Blood Changes Following Splenectomy** (Chart 2, Table 4) (1) **Hemoglobin and Red Blood Cells** The transfusion of 500 cc before splenectomy raised the hemoglobin to 48 per cent and the transfusion given immediately after the operation produced a further rise to 60 per cent and a rise to 3,232,000 red blood cells. This gradually dropped during the first four days to 38 per cent hemoglobin and 2,832,000 red blood cells. Improvement then began and at the last examination (April 6, 1923) the hemoglobin was 81 per cent and the red blood cells were 4,840,000. Normoblasts and Howell-Jolly red cells were occasionally present.

(2) **White Blood Cells** Just before the operation there was a leukocytosis of 22,000, six hours after the operation the leukocytes were 36,000, and on the following day they rose to 55,000. The differential blood picture after the

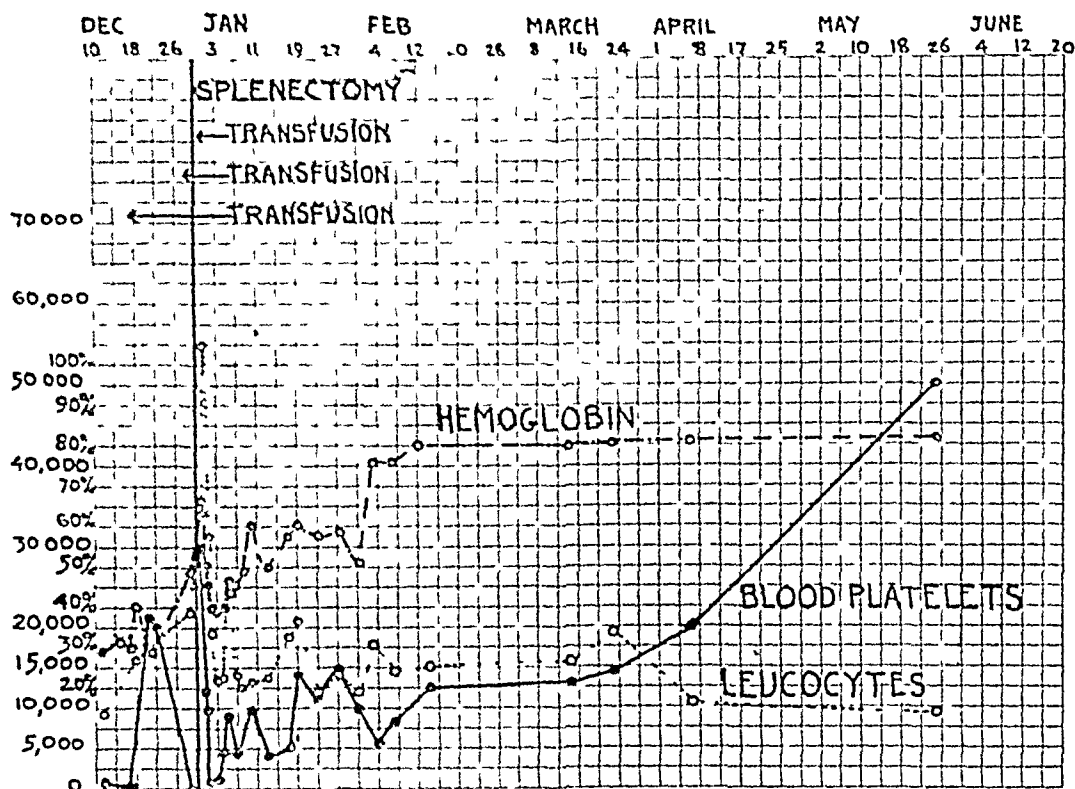


Chart 2 (Case 2) — Variations of the hemoglobin, leukocytes and blood platelets following splenectomy

postoperative polynucleosis showed a persistent monocytosis (increase of the large mononuclears and transitionals)

(3) **Blood Platelets** The day following the operation there was a slight rise to 31,200, then a gradual fall to 1,000 on the third day after the operation. After this there was a gradual increase to 10,000, and then to about 20,000. The morphology remained about the same. The day following the operation a few giant blood platelets appeared in the smears.

(4) **Bleeding Time** For a month and a half this was prolonged, usually over two minutes, and even as long as twelve minutes. This became normal (two to three minutes).

(5) **Tourniquet Test (Capillary Resistance)** This was constantly positive until the third month after the operation. It then became constantly negative.

(6) **Clot Retraction** There was no clot retraction for six weeks after the operation. This appeared on Feb 14, 1923, and slight clot retraction remained

Dec 31, 1922 The blood pressure was systolic 95, diastolic 70 The pulse rate was 160, later, 132 Digifolin, 15 minims, was administered every three hours Rectal drip was given for two hours alternated with two hours when it was not given

Jan 1, 1923 The general condition was much improved There was slight abdominal pain, especially in the wound, and also slight precordial pain There was no bleeding

Jan 2, 1923 There was slight nose bleed once during the night

Jan 3, 1923 There was nose bleed once during the day

Jan 4, 1923 There was slight bleeding again from the nose, a few drops of blood oozed out and stopped immediately, never oppressive nor profuse as on previous occasions

Jan 7, 1923 There was a slight serosanguinous discharge from the wound

Jan 8, 1923 The sutures were removed, accompanied by bleeding easily controlled with epinephrin

TABLE 4—Case 2, Blood Examinations After Splenectomy

	Hemo- globin, Per- cent- age	Red Blood Cells	White Blood Cells	Plate- lets	Poly- morpho nuclears, Per- cent- age	Lym- pho cytes, Per- cent- age	Mono cytes, Per- cent- age	Coag- ula- tion Time, Min	Bleed- ing Time, Min	Capillary Resis- tance Test	Clot Retraction
After 2 hours*	64	3,232,000	36,000	31,200	93.6	2.6	3.3		3		
12/31/22	51	2,888,000	55,000	12,000	94.0	1.3	4.3				
1/ 1/23	46	2,992,000	30,400	10,000	90.0	3.0	7.0		5		
1/ 2/23	40	2,896,000	19,400	1,000	89.0	4.0	6.6		10		
1/ 3/23	38	2,832,000	14,000	2,000	82.0	7.3	9.0		10		
1/ 4/23	40	2,656,000	14,400	4,800	80.3	7.0	10.3		5		
1/ 5/23	47	2,884,000	27,000	8,000	74.3	10.3	13.3	10	4	Slightly positive	None
1/ 6/23	46	2,936,000	14,000	4,000	75.3	14.0	7.0		8		
1/ 8/23	49	3,450,000	12,000	4,000	72.0	15.6	8.3		10		
1/10/23	60	3,992,000	13,200	10,000	73.6	14.3	9.6	7	8	Slightly positive	None
1/13/23	56	3,520,000	14,400	4,000	75.3	15.3	6.3			Slightly positive	
1/19/23	60	4,800,000	21,000	14,000	72.0	18.0	8.0		10	Slightly positive	
1/27/23	58	4,536,000	14,400	14,000	59.3	27.0	11.0	11	8	Slightly positive	None
1/31/23	59	4,480,000	12,000	10,000	53.3	40.3	6.3				
2/ 3/23	76	4,808,000	18,000	6,000	57.3	28.6	11.0		4		
2/ 7/23	76	4,816,000	14,600	8,000	57.0	32.3	8.0	12	3	Slightly positive	None
2/14/23	80	4,704,000	15,000	12,000	58.6	34.6	4.3	6	3	Slightly positive	Present but slight
3/23/23	80	4,736,000	18,200	14,000	49.6	44.6	4.3	8	3	Negative	Present
4/ 6/23	81	4,840,000	10,400	20,000	48.0	42.3	9.0	12	2	Negative	Present
5/26/23	83	5,120,000	9,000	50,000	44.3	41.3	10.6	9	2	Negative	Present

\* Done after a blood transfusion

Jan 11, 1923 All sutures were out There was slight bleeding from the wound not controlled by thromboplastin Epinephrin controlled the bleeding more satisfactorily There was slight nose bleed which was stopped with epinephrin

Jan 19, 1923 The patient was out of bed Many petechiae appeared on the legs and a few on the right lower conjunctivae

Feb 3, 1923 A few petechiae on the face and lower legs appeared from time to time The gums had improved, there was no sponginess and no bleeding

Feb 8, 1923 There were hypostatic petechiae on the legs only The general condition was excellent The hemoglobin content was 76 per cent

Feb 14, 1923 For the first time clot retraction was present There was a thrombocytopenia and slightly positive capillary resistance test The petechiae were disappearing from the legs There had been no hemorrhages since Feb 9, 1923

exert an influence on two important properties of the blood platelets, namely, the one which produces clot retraction and the property of the blood platelets to agglutinate to form thrombi. These properties may be restored immediately after the removal of the spleen or by a later steady development.

We believe that the main process is not entirely an inhibitory or a destructive one on the part of the spleen in this disease, but some damaging and to a certain extent a destructive mechanism exerted by the reticulo-endothelial system on the blood platelets. The damaging mechanism possibly resides in the reticulo-endothelial system, mainly in the spleen, hemolymph nodes, liver, lymph nodes and bone marrow. Splenectomy, while it does not influence the number of blood platelets in the circulation, induces a cessation of capillary hemorrhage. The influence of the reticulo-endothelial system in modifying the quality of the platelets varies in intensity from time to time, but it is always present. When an increase in function occurs it gives rise to the severer types of this disease, or when diminished, a milder action is manifest as indicated when hemorrhage follows ordinary trauma.

Blood platelets have certain important vital properties. First, they furnish cytozyme (Bordet<sup>18</sup>) for the formation of the blood clot. Any alteration of this property leads to the condition of hemophilia in which the coagulation of the blood is markedly prolonged on account of the delay in the proper formation of cytozyme—the initial step in the coagulation of the blood. In essential thrombocytopenia cytozyme is rapidly formed, but the amount is necessarily diminished on account of the fewer platelets, and the clear citrated purpuric plasma does not clot after standing several hours, on account of the sedimentation of the platelets.

Second, the blood platelets have an agglutinative property (Bizzozero<sup>19</sup>) by virtue of which they rapidly adhere to cut or injured surfaces of the tissues, resulting in the formation of a thrombus. The minimum number of blood platelets necessary for this action on cut skin capillaries is low compared to what occurs in the essential thrombocytopenic state (Table 3). In pernicious anemia, leukemia and in a few cases of secondary anemia, we have found platelet counts below 10,000 without any prolongation of the bleeding time. In some cases of essential thrombopenia the bleeding time is prolonged, although the blood platelets may be as high as 250,000. In the rare condition of thrombasthenia the bleeding time is greatly prolonged, although the

18 Bordet, J. *Bull. Johns Hopkins Hosp.* **32** 213, 1921.

19 Bizzozero. *Virchows Arch. f. path. Anat.* **90** 261, 1882.

present although the blood platelets remained low. It is interesting to note that the blood of this patient never showed clot retraction on previous examinations.

*Summary*—This was a case of chronic thrombocytopenia of four years' duration. The patient's condition became worse as time went on, the bleeding was more frequent and more severe. Splenectomy brought about a turn for the better, and the patient has steadily improved since.

The patient was again seen in April, 1923. He had had no hemorrhages since he left the hospital. He had gained weight and strength steadily. Static purpura of the legs did not occur. The examination of the blood still showed a thrombocytopenia (blood platelets, 22,000), but all other evidence of the previous condition was absent. The capillary resistance test was negative and clot retraction was present.

#### DISCUSSION

A study of the blood changes following splenectomy in our cases brings us a step nearer to the solution of the underlying factors in the production of the thrombocytopenic syndrome. This tends to show that, first, the inhibitory action of the spleen on the megakaryocytes of the bone marrow suggested by Frank,<sup>5</sup> or, second, the thrombolytic or blood platelet destructive action of the spleen as suggested by Kaznelson<sup>17</sup> are not explanatory theories of the pathogenesis of this disease. The first case described by Kaznelson probably belongs to a different subgroup of the thrombocytopenic purpuras, because he found large numbers of blood platelets in the sinuses of the spleen. Examination of our spleens showed neither in smears nor in cut sections any abnormal increase of the blood platelets, but, on the contrary, a marked diminution of the blood platelets was present. While the spleen apparently assumes a thrombolytic function normally, there is little evidence outside of Kaznelson's and a few other observations to show that in this type of purpura this supposed action of the spleen is increased.

It is remarkable in all these cases that with the removal of the spleen active hemorrhage immediately stops. This sudden cessation of hemorrhage would indicate that the function of the spleen in these cases could not be taken up so quickly by any vicarious action of other members of the hematopoietic or reticulo-endothelial system. It might indicate that when the spleen was removed some agency became active in inducing the capillaries to contract so as to stop all bleeding. Therefore it tends to show that the normal spleen has some controlling mechanism on capillary activity through the medium of the blood platelets.

From our observation it would appear that the spleen does not function in inhibiting the activities of the megakaryocytes in the production of platelets, even though the removal of the spleen is followed by their temporary increase in the circulating blood, because the blood platelets quickly return to their diminished number or even to a lower level. It would appear, however, that the spleen in these cases does

## CONCLUSIONS

1 Splenectomy has a definite curative influence on the hemorrhagic factor of chronic thrombocytopenia

2 It does not seem to be a determining factor in restoring the normal number of blood platelets to the circulating blood

3 The disease seems to be associated with a disturbed function of the capillary wall in addition to a disordered state of the blood platelets, or it is a result of the diminution of the latter. This is evidenced by the occurrences of purpuric hemorrhages in the skin of the legs on prolonged standing and by the presence of a positive capillary resistance test. With the removal of the spleen the capillary resistance test disappears, as does the static purpura

4 After splenectomy the quality of the blood platelets is restored, as is demonstrated by the reappearance of clot retraction and diminution of the bleeding time to normal

blood platelets are always over 100,000. Third, clot retraction is also an important indicator of the condition of the platelets. Clot retraction may appear with less than 20,000 blood platelets. In essential thrombocytopenia this phenomenon is usually absent, although the platelets may be over 50,000, and in thrombasthenia it is absent with even a greater number of platelets.

This peculiar damaging action on the blood platelets by some element in the spleen and other organs does not account for the diminished number of blood platelets in the circulating blood. Following the initial rise after splenectomy they fall to their low figures, so that we must assume that there is some fault in their formation. The megakaryocytes are not diminished in number in the bone marrow in essential thrombocytopenia, but the fragmentation of the pseudopodia of these large cells does not take place properly, because the blood platelets in this disease are very large and irregular. Normally, a certain number of blood platelets are destroyed daily in the spleen. The results of such a destructive action in a case with defective blood platelet formation possibly leads to a further diminution of their number and to an altered function of these bodies.

In some of the patients with thrombocytopenia who were operated on, the hemorrhagic tendency returned, but it was not as severe as formerly. Here we must assume that the remaining reticulo-endothelial system has taken up the function of the spleen and has exerted its dangerous influence on the few blood platelets formed. To combat this we must turn our attention to some methods of inhibiting the activity of this system. At present we are using roentgen-ray therapy and also foreign protein injections (milk, Gram<sup>20</sup>) with encouraging results in some unoperated cases. Their use in splenectomized cases may prove beneficial if there should be a recurrence.

The removal of the spleen is followed by a gradual return of the agglutinative and retractive properties of the blood platelets, although its removal has no effect on their formation. On the integrity of the blood platelets depends also the proper tonus and contractility of the capillaries. We need not go into the question of the relation of vascular constriction to the quality of the blood platelets. O'Connor,<sup>12</sup> Janeway<sup>13</sup> Hirose<sup>21</sup> and others have shown this intimate relation. It is noteworthy that the capillary resistance test in our cases was positive for a long time and was slightly positive occasionally in Case 1 until April 24, 1923. It is now persistently negative in this case.

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20 Gram, H. C. *Ztschr f klin Med* **95** 51, 1922.

21 Hirose, K. Relation Between the Platelet Count of Human Blood and Its Vasoconstrictor Action After Clotting, *Arch Int Med* **21** 605 (May) 1918.

10 Gulland and Goodall<sup>7</sup>) Hence it is obvious that a transitional count must be at least 5 to be regarded as high

The table shows that among the eleven untreated patients there were only two that had transitional counts of more than 5 per cent Of the eight patients that had received treatment, there were four with transitionals higher than 5 per cent and two with just 5 per cent Hence, eight out of eighteen cases showed an increase in transitionals, two of these were only a little higher than normal

#### TOTAL COUNTS

When the cases are arranged in order of total white cell count, there is no apparent relationship to the length of the disease The highest white count was 13,000 The highest percentage of neutrophils are found in the higher counts

#### PLATELETS

In Bunting's first paper he mentions<sup>1</sup> platelet counts, all of which were high He then compares these smears with other smears from cases of Hodgkin's disease and is convinced that the platelets are high, and in his later articles<sup>1</sup> he estimates the number of platelets by examining the smear A skilled observer may well be able to obtain satisfactory results from an examination alone, but I have found it much more accurate to count the platelets, as one may occasionally be deceived by the thickness of the smear or by a tendency of the platelets to gather in groups, which is misleading In some of the cases with high platelet counts large clumps of platelets were noticed, but no megalokaryocytes were observed

*Platelet Counting*—The method used at first was that described by Ottenberg and Rosenthal<sup>8</sup> This method had several advantages (1) simplicity of solution, (2) stability, and (3) the red cells were present This is advisable, as they give an excellent check on the preparation If the Wright and Kinnicut<sup>9</sup> method is used, one has only the platelets themselves, and errors are more probable

The method recently described by Rees and E. E. Ecker<sup>10</sup> has also been tried, and has been found to give good results Other

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7 Gulland, Lovell G., and Goodall, Alexander The Block, New York, E. B. Treat & Co., 1912, p. 61

8 Ottenberg, R., and Rosenthal, Nathan A New and Simple Method for Counting Blood Platelets, J. A. M. A. **69** 999 (Sept. 22) 1917

9 Wright, James Homer, and Kinnicut, Roger A New Method of Counting the Blood Platelets for Clinical Purposes, and Some of the Results Obtained With It, J. A. M. A. **56** 1457 (May 20) 1911

10 Rees, Maynard H., and Ecker, E. E. An Improved Method for Counting Blood Platelets, J. A. M. A. **80** 621 (March 3) 1923



# BLOOD COUNTS IN HODGKIN'S DISEASE

## REPORT OF CASES<sup>1</sup>

KENNETH R McALPIN, M D

NEW YORK

In 1911 and 1914, C H Bunting<sup>1</sup> published his papers on the blood count in Hodgkin's disease. He believed that the blood count was of real value from a diagnostic point and showed (1) an increase in blood platelets, and (2) an absolute increase in the transitional leukocytes. Although no one appears to have attempted to disprove directly the work of Bunting, of late there seems to be a good deal of doubt as to the accuracy of his conclusions. Among those who doubt the diagnostic value of the blood count are Janeway<sup>2</sup> and Pepper<sup>3</sup>.

During the last four years, I have studied all of the cases of Hodgkin's disease in the Presbyterian Hospital wards and outpatient department. There have been eighteen cases that were diagnosed as Hodgkin's disease. Only those cases that were diagnosed by microscopic section were used in the series.

Blood counts were all made by myself, as a rule, 500 cells were counted. The only exceptions were Cases 7, 15 and 16. In these cases, 300 cells were counted. Both Hasting's and Wilson's stains were used and were equally satisfactory. Large mononuclears and transitionals (as described by Bunting<sup>1</sup>) were classified together, as it is frequently difficult to make a satisfactory distinction between them. The number of transitionals in normal blood varies considerably (from 2 to 4, Wood<sup>4</sup>, from 3 to 5, Webster<sup>5</sup>, from 6 to 8, Naegeli<sup>6</sup>, from 3 to

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\*From the Department of Medicine, Columbia University, College of Physicians and Surgeons, and the Presbyterian Hospital, New York City.

1 Bunting, C H. Blood Platelets and Megalokaryocytes in Hodgkin's Disease, *Bull Johns Hopkins Hosp* **22** 114, 1911. The Blood Picture in Hodgkin's Disease, *Ibid*, p 369. Hodgkin's Disease, *Ibid* **25** 173, 1914.

2 Janeway, T C. A Case of Hodgkin's Disease with Skin Eruption, *Med Clin North America*, July, 1917, p 20.

3 Pepper, O H. Perry. Hodgkin's Disease with Jaundice as an Early Symptom, *Med Clin North America*, March, 1920, p 1449.

4 Wood, T C. Chemical and Microscopical Diagnosis, New York, D Appleton and Company, 1917, p 103.

5 Webster, Ralph W. Diagnostic Methods, Philadelphia, P Blakiston's Sons and Company, 1920, p 560.

6 Naegeli, O. Blutkrankheiten und Blutdiagnostik, Leipzig, Von Vert, 1912, p 186.

in the eighteen cases, both treated and untreated, only seven have high platelet counts

#### THE WASSERMANN REACTION

In fourteen cases, the Wassermann tests were negative, in three doubtful Case 7, alcohol —, cholesterin ++, Case 9, never positive in both antigens, but the test was performed three times with the following results alcohol —, cholesterin ++, alcohol ++, cholesterin —, alcohol +++ cholesterin —, Case 15 the diagnosis was tabes, but the Wassermann test was never definite, in other words, the blood Wassermann was negative three times and doubtful twice, as follows alcohol ±, cholesterin ++, alcohol —, cholesterin +, both after provocative doses of arsphenamin The spinal fluid was negative twice

In Case 4 a private patient, the Wassermann test was not performed

Strangely enough, the treated patients show both more higher platelet counts and more increased transitionals than the untreated

#### SUMMARY

1 From this series of eighteen cases, it would not be possible to diagnose Hodgkin's disease from examination of the blood

2 In this series, platelet counts were high in seven and transitionals were high in eight

3 It is advisable to count platelets, when possible, as estimating the number from the smear is not always reliable

4 The length of illness apparently has no bearing on the total white count

methods have been described by Cramer,<sup>11</sup> Buckman,<sup>12</sup> Gram<sup>13</sup> and Kristenson<sup>14</sup>

It was found more convenient to use a counting chamber of 0.02 mm in depth rather than the usual 0.1. If the dilution was 1 to 200 and a square mm was counted, the factor would be  $1/50 \times 1/200$  or  $1/10,000$ . This is, of course, too high, and was reduced by counting not less than three different preparations of 1 square mm each.

Writers vary somewhat in their estimation of a normal count. Wood<sup>15</sup> suggests from 200,000 to 400,000, Webster<sup>16</sup> suggests 250,000, while Naegeli<sup>17</sup> quotes five different observers, the average being between 200,000 and 250,000. Hence, it would seem reasonable to assume that 300,000 is approximately a normal figure.

<i>Before Treatment</i>											
Case No	Apparent Time Since Onset	White Blood Cells	Platelets	Neutrophils	Eosinophils	Lymphocytes	Transitionals	Leukocytes	Mycobacteria	Basophils	Termination
4	3 months	13,000	680,000	89.6	3.0	4.6	2.2	0.6			Dead
8	3½ years	11,000	400,000	47.8	7.8	34.8	7.0	1.8	0.4	0.4	Dead
5	1½ years	10,900	38,000	86.2		9.4	3.6	0.6		0.2	Dead
7	3 months	10,000	150,000	78.4	0.3	18.3	3.0				Living
15	6 weeks	8,800	230,000	62.0	12.0	22.0	3.7			0.3	Lost
16	4 years	7,200	210,000	69.0	0.6	26.4	3.7			0.3	Living
12	1 year	6,000	200,000	61.4	1.3	32.4	4.6			0.3	Dead
6	1½ years	4,900	150,000	67.4	2.6	26.0	3.2			0.8	Dead
17	8 months	4,200	150,000	51.4	5.0	31.3	3.0			0.3	Living
13	2 months	4,000	180,000	71.6		20.6	7.4	0.2	0.2		Dead
<i>After Treatment</i>											
11	5½ years	10,000	340,000	79.6	0.2	3.0	17.0			0.2	Dead
10	5 months	8,200	350,000	71.8	7.4	17.6	7.6			0.6	Living
9	2 years	7,000	370,000	76.4	4.8	13.4	5.0	0.2		0.2	Living
1	1 year	6,000	550,000	78.6	3.2	6.8	11.2			0.2	Dead
2	7 months										
	1 year	5,700	300,000	78.0	2.2	11.2	6.6	2.0			Living
	4 months										
18	3 months	4,500	280,000	65.8		31.0	2.8	0.4			Living
3	15 months	4,300	470,000	70.8	3.8	20.0	3.6		0.6	1.2	Dead
14	4 months	2,000	45,000	32.5		62.0	5.0	0.5			Living

The table shows that in the untreated cases, only two are above this limit while in the treated cases there are five above 300,000 and one just 300,000, but of these three are less than 400,000. Therefore,

11 Cramer, W., Drew, A. H., and Mottram, J. C. On Blood Platelets. Their Behavior in "Vitamin A" Deficiency and After "Radiation," and Their Relation to Bacterial Infections, *Proc Roy Soc, B* **93** 449, 1922.

12 Buckman, T. E., and Hallisey, Joseph E. Studies in the Properties of Blood Platelets (A New Method for Counting Platelets), *J A M A* **76** 427 (Feb 12) 1921.

13 Gram, H. C. On the Platelet Count and Bleeding Time in Diseases of the Blood, *Arch Int Med* **25** 325 (March) 1920.

14 Kristenson, A. New Method for Counting Blood Platelets in Man, *Acta Med Scand* **57** 301, 1922.

15 Wood, T. C. Chemical and Microscopical Diagnosis, New York, D Appleton and Company, 1917, p 100.

16 Webster, Ralph W. Diagnostic Methods, Philadelphia, P Blakiston's Sons and Company, 1920, p 580.

17 Naegeli, O. Blutkrankheiten und Blutdiagnostik, Leipzig, Von Veit, 1912, p 344.

stration of one teaspoonful of the official dilute hydrochloric acid with each meal. The acid was given in 6 or 8 ounces of water, lemonade, orangeade, iced tea or, preferably, buttermilk. The results of treatment are particularly interesting in that Patient 3 is subjectively cured, Patients 1 and 5 are apparently well, and Patient 6 is greatly improved. Patient 4 discontinued his treatment, and later wrote that he was unimproved. Patient 7 is growing progressively worse, but it is learned that he took the hydrochloric acid in inadequate amounts and later discontinued it. Patient 2 took his hydrochloric acid regularly, but died two and one-half years after his treatment was started of progressive spinal cord symptoms. A brief abstract of the histories of these seven cases follow.

#### REPORT OF CASES

CASE 1—Mrs. M., married, aged 51 years, was seen on May 21, 1918, complaining of a burning creeping sensation in the feet and legs of six months' duration. These paresthesias were worse at night and kept her from sleeping. She had had no indigestion since her gallbladder was removed in 1913, except for a morning diarrhea for the past six years. Her tongue was clean but not bald.

The patient returned for observation Jan. 4, 1919. She had taken hydrochloric acid regularly until November, 1918, and the paresthesias in the feet had improved. She then stopped the acid and the burning in the feet returned. She had then resumed the acid but the burning sensation in the feet had persisted for some time. Her diarrhea stopped when she was first put on the hydrochloric acid and her bowels were regular until she stopped the acid, when they became loose again.

The patient was last heard from on Feb. 14, 1923, when she wrote, in response to an inquiry addressed to her home in another state, as follows: "I have taken the hydrochloric acid regularly, only leaving it off occasionally to watch the effect. I find that my feet burn if I leave it off more than two days. I still take the dose prescribed by you. I have not had a doctor since I saw you, and do not know whether I am anemic but I seem to be well."

CASE 2—Mr. D., married, aged 65 years, a retired farmer, was first seen on March 11, 1919, complaining of numbness in the hands and feet of four months' duration. His past health had been excellent with no history of acute infections, except an attack of gonorrhea at the age of 20 years. He gave a history of sciatica ten years previously, with gradual recovery and no recurrence. His appetite was good, and he gave no history of digestive disturbance except occasional slight diarrhea and, more recently, some flatulence. He had used tobacco and liquor in moderation in the past but not in recent years. There was no loss of weight. His first symptom was numbness and tingling in the fingers and toes on the left side, with similar involvement, a few days later, on the right side. A little later he noticed numbness on the inner aspects of both thighs and then over the abdomen up to the rib margins. He had had no darting pains, no muscular weakness, no difficulty in walking in the dark and no incontinence of the sphincters. Smooth objects, like apples, felt rough to his fingers. He had observed no objective change in the extremities. The tongue was clean and distinctly red about the margins and tip.

He was next seen in October, 1919, when he said that his numbness was worse and affected the hands, forearms, feet, legs and hips. He had difficulty in picking up small objects and in writing. (He constantly rubbed the palmar

# THE ETIOLOGIC RELATION OF ACHYLIA GASTRICA TO COMBINED SCLEROSIS OF THE SPINAL CORD

THE RELIEF OF SYMPTOMS FOLLOWING ADEQUATE HYDRO-  
CHLORIC ACID THERAPY<sup>1</sup>

DOUGLAS VANDERHOOF, M D

RICHMOND, VA

In a recent clinical study of 451 patients with achylia gastrica, there were twenty-nine with definite evidence of combined sclerosis of the spinal cord. Of these twenty-nine patients, fourteen had pernicious anemia, one had pellagra, and in seven the observations were unsatisfactory or incomplete, leaving seven patients that form the basis of this article.

## SUMMARY OF THE CASES

These seven patients with combined sclerosis of the spinal cord all received complete clinical and laboratory studies. The gastric analyses were made by the fractional method, one examination being made in Cases 4, 6 and 7, two examinations in Cases 1, 2 and 5, and seven gastric analyses were made in Case 3. Blood counts were made in all cases, together with a study of the stained smears, and showed no evidence of pernicious anemia except the late developments in Case 7. The Wassermann reaction on the blood serum was negative in all cases, and the spinal fluid was examined and found normal in Cases 2, 3 and 5. The blood sugar was examined and found normal in Cases 3, 5 and 6, and the nitrogen content of the blood was found normal in Cases 3, 5, 6 and 7.

Foci of chronic infection were sought for in all cases, in Patient 7 none could be found, Patient 3 had infected tonsils which were removed, Patient 2 had a mild prostatitis which cleared up on treatment, in Cases 1, 2 and 3 there were apical abscesses about certain teeth, and these teeth were extracted, Patient 4 showed marked pyorrhea alveolaris, Patient 5 had had all of his remaining teeth extracted two months before the onset of his paresthesias, and he said that several of these teeth were abscessed, Patient 6 had lost all his teeth except four, and these showed extensive pyorrhea. There was moderate arterial hypertension in Cases 3 and 6, in the five remaining cases, the blood pressure was normal.

Treatment in each case consisted in the removal of such foci of infection as could be found, and the regular and persistent admini-

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<sup>1</sup>Presented before the Thirty-Eighth Session of the Association of American Physicians, Atlantic City, N J, May 1-2, 1923

never severe, usually occurred two or three hours after meals, and he was constipated. He had had no nausea, vomiting or flatulence and gave no history of acute pain or colics. The paresthesias were described as a peculiar crawling sensation in the legs with a burning in the feet and ankles. His tongue was clean. In response to an inquiry, the patient wrote, under date of March 14, 1923, from his home in the country that he had "not been able" to take the acid, that he continued to suffer with the burning sensation in his legs, and that his digestion was poor.

CASE 5—Mr M, aged 61, a lawyer, single, was seen on Nov. 28, 1921, complaining of numbness and loss of control of the legs and hands. He used to have a good deal of indigestion, and beginning in 1891 he had diarrhea with undigested food in his stools for two years. (He described a rather typical gastrogenous diarrhea.) His digestion then improved until 1914, when he again developed diarrhea and weakness. Gastric analysis at that time showed a complete achylia. (This fact was confirmed by communication with the physician who examined him at that time.) He was given small doses of hydrochloric acid but did not take it regularly. His appendix was removed in 1915, and since that time his bowels had been regular, and he regarded his digestion as good. His past history was otherwise unimportant. He smoked and drank in a moderate way.

In March, 1921, the patient had some rheumatic pains in the lower legs. All his remaining teeth were extracted in August, 1921. He said that several of these were abscessed. Early in October, 1921, he noticed a numbness and peculiar feeling in the left great toe. This numbness soon spread to the other toes and to the foot, and soon started in the same way in the right foot and gradually spread up both legs to the groins, he then developed a tight feeling about the trunk as if a cord were tied around the waist. Shortly after the onset of the paresthesias in the feet, the same numbness developed in the fingers of both sides and then spread over the hands. He complained that he did not have proper control of the arms and legs, and had difficulty in writing and in walking. He had no headache, vertigo or unconscious attacks. His mouth was not sore. He wore his shoes unlaced because of the paresthesias and was constantly rubbing his thumb and fingers together (as did Patient 2), but he had no tremors or pill-rolling motion. The tongue was clean but not bald. He was again seen on Dec. 28, 1921. His weight was the same and his general condition was unchanged, except that he said the feeling of tightness around his waist had risen a little higher on his trunk and was then noticed around the lower part of the chest.

The patient returned for examination, by request, in April 1923. He said that he regarded himself as well and was actively engaged in his law practice. He said that the greatest improvement had occurred in his hands, in which the numbness had practically disappeared. The girdle sensation had also disappeared, together with the constricted feeling across the hips and lower abdomen. He had no difficulty in writing or in walking. He continued to be conscious of some numbness in his feet and legs. He had taken the hydrochloric acid regularly. His appetite was good, he had no indigestion or sore mouth, his bowels were regular. Examination showed that the physical signs persisted in the lower extremities with absent deep reflexes and definite loss of sensation to touch with diminished pain sense, especially over the inner aspect of the legs. Gastric analysis was repeated at this time and showed free hydrochloric acid absent at the end of thirty, forty-five and sixty minutes. Blood count showed red cells 4,216,000, hemoglobin, 85 per cent, differential leukocyte count and morphologic picture normal.

CASE 6—Mr S, aged 71, married, a farmer, was seen on June 28, 1922, complaining of intense burning in the feet of four months' duration. His past history showed that his general health had been excellent, he had had some indigestion as a younger man, characterized by sour stomach, but had had no

surface of the thumb of each hand against the palmar surface of the fingers) He was a little unsteady on his feet, but he said he had no difficulty in walking He had no pain or stiffness in his back He had taken his hydrochloric acid regularly in teaspoonful doses with his meals He said that he had suffered with sore tongue for years before taking this acid, but not since He had no further diarrhea His digestion was good He had no urinary disturbances The tongue was moist, red and clean

The patient was next seen in January, 1920 He had lost 9 pounds (4.1 kg) since March, 1919 His general condition appeared to be unchanged The neurologic findings indicated that the trouble had been progressive

In May, 1921, I saw the patient for the last time, at his home in a distant part of the state, and he then showed a flaccid paraplegia with marked ataxia, absent deep reflexes and involvement of the sphincters He died in October, 1921 For three weeks prior to his death he had difficulty in swallowing and retention of urine His family physician reported that at no time did he present any appearance of pernicious anemia, and that several blood counts made during the last few months of his life showed no reduction in either the red cell count or in the hemoglobin It was understood that the patient took full doses of hydrochloric acid during practically the whole period of his illness

CASE 3—Mrs F, aged 42 years, first consulted me on Nov 15, 1919, complaining of a sensation of numbness which began in the feet in February, 1919, and then gradually extended up the legs and trunk to the waistline A little later she developed numbness in the hands and arms, extending up to the elbows She said that the soles of her feet felt as if she were walking on something stiff, not like cotton She said she had difficulty in walking, could not manage her feet well, was inclined to catch hold of things when she walked, and that she fell easily She had difficulty in picking up small objects and in fastening her clothes and often dropped things She said she had no tingling and no loss of touch sensation About three years previously she had developed a sore mouth, and since then the tongue had been red and inflamed

Her past history showed that she had had malaria at 17, diphtheria at 21, attacks of tonsillitis but none in the past eight years, and influenza in 1918 The appendix and one ovary were removed in 1904 She had had no indigestion except flatulence The bowels were constipated She had acute cystitis with hematuria in June, 1919 At that time she had increased blood pressure The tongue was moist, red and clean

The patient was again seen in May 1920, October, 1920, June, 1921, June, 1922, and March, 1923 By October, 1920, the numbness in the extremities had disappeared, except for slight paresthesia in both feet, and she had no further stomatitis Since that time, the patient had considered herself entirely well When last seen in March, 1923, she said she had no numbness, except occasionally when tired she might notice a feeling of sleepiness or heaviness in her feet and legs Her appetite was splendid, and she had no indigestion She was again completely examined, and her seventh gastric analysis showed a complete achylia It was interesting to note that, in spite of the disappearance of subjective symptoms, the physical signs persisted All of the deep reflexes were exaggerated, there was an exhaustible ankle clonus, and sensation to touch was greatly impaired from the feet up to a point midway from the ankle to the knee on each side She had taken hydrochloric acid regularly since 1919, and she was advised to continue it

CASE 4—Mr M, a farmer, aged 60 years, married, was seen on April 13, 1920, complaining of stomach trouble and a crawling sensation in his legs His past history included malaria in 1910 grip in 1905, and rather frequent sore throat Otherwise it was unimportant He had used tobacco freely, but very little liquor He was 12 pounds (5.4 kg) below his usual weight

His present illness dated back one year previously, when he developed pain in the abdomen and paresthesias in the extremities The epigastric pain was

monograph,<sup>1</sup> states that the clinical features of subacute combined degeneration of the spinal cord are usually strikingly distinct in that subjective sensations, such as tingling, numbness and burning, occurring usually at the periphery of the extremities, are early, obtusive and persistent symptoms, and are accompanied or followed by the development of a paraplegia which may be of a spastic type, or of a flaccid and ataxic type, or of a mixed type, according to the degree of affection of the lateral and of the posterior columns in each case. The deep reflexes are present exaggerated or absent, according to the relative condition of these columns. Loss of sensibility of peculiar distribution occurs, which has a "glove and stocking" distribution on the extremities and a segmental distribution on the trunk. In the late stages of the malady the paraplegia tends to become complete and of the flaccid type with loss of the deep reflexes. It is a disease of adult life, most of the cases occurring in the fifth, sixth and seventh decades. The sexes are equally affected, heredity is not a factor, and syphilis plays no part in the etiology.

#### THE RELATION OF PERNICIOUS ANEMIA TO COMBINED SCLEROSIS OF THE SPINAL CORD

The intimate relation of pernicious anemia to combined sclerosis of the spinal cord has been emphasized by many writers, and the earlier authors believed that the degeneration in the nervous system was the result of vascular changes consequent on the anemia. This point is negatived, as pointed out by Collier, by the facts that some cases of combined spinal sclerosis progress to a fatal issue without any evidence of anemia, and that in others the nervous manifestations may become severe long before any anemia is evident. Collier concludes that certain experimental evidence as well as the clinical and pathologic features of the disease suggest that the anemia and the degeneration of the nervous system are not dependent the one on the other, but that they are the concomitant but not necessarily synchronous results of one and the same cause.

#### ASSOCIATION OF ACHYLIA GASTRICA WITH PERNICIOUS ANEMIA

The almost invariable association of achylia gastrica with pernicious anemia has been recognized for many years. Among the more recent reports is that of Levine and Ladd,<sup>2</sup> who report an absence of free

1 Collier, J. *Intrinsic Diseases of the Spinal Cord*, Oxford Medicine, New York, Oxford University Press, 5 356, 1921.

2 For a good bibliography and an excellent discussion of this subject, based on a study of 150 patients at the Mayo Clinic, see article by Woltmann, H. W. *The Nervous Symptoms in Pernicious Anemia*, *Am J M Sc* **157** 400, 1919.

3 Levine, S. A., and Ladd, W. S. *Pernicious Anemia, a Clinical Study of 150 Consecutive Cases with Special Reference to Gastric Anacidity*, *Bull. Johns Hopkins Hosp* **32** 254, 1921.



digestive disturbance in the past twenty years. His bowels had always been regular. He had used tobacco, but no liquor. He was underweight about 10 pounds (4.5 kg). In the latter part of February, 1922, he suddenly developed a burning sensation in the soles of both feet, without any redness or swelling. Then he gradually developed numbness in both legs with a sensation as if water were dripping on them, and some difficulty in walking. He had also developed burning in the ends of the fingers and some burning spots on the face. The burning in the feet was distressing, and at first was constant day and night, but after taking some medicine from his home physician, he had been able to secure some sleep at night. He said that his hands felt drawn and cramped. The tongue was slightly coated.

On March 16, 1923, the patient's physician wrote: "Mr. S., asked me to reply to your letter and to say that he weighs fifteen pounds more than he has for thirty years, that he has taken his hydrochloric acid every day since he saw you, except eight days, that his feet do not burn at night but do burn some in the daytime, that he eats anything and as much as he wants." The physician added that the patient looked a good deal better and was not anemic.

CASE 7—Dr. X, aged 64, married, was first seen by a colleague on June 5, 1922, and the case has since then been followed by both of us. The patient's past health had always been good. He had had influenza in 1918 and again in 1921, otherwise he had had no illnesses and no acute infections since childhood. He had been a moderate smoker but had never used liquor. He dated the onset of his present illness to an attack of influenza in October, 1921, although he had not felt well since December, 1920, when, after some exertion, he had had a brief attack of dizziness, confusion and a feeling of prostration. About October, 1921, he began to suffer from distressing paresthesias, with numbness in the feet, legs and hands. He became nervous, anxious and irritable and had some dizziness. He had developed difficulty in using his fingers for finer movements, and his gait had become uncertain. He had had no headache or convulsive attacks, no disturbances of the special senses, and he gave no history of digestive disturbances or any loss of weight. Gastric analysis was made because of the paresthesias and evident cord changes and showed free hydrochloric acid absent at thirty and forty-five minutes after an Ewald test breakfast after which time the stomach was found empty.

The patient was seen again on Dec. 16, 1922. He had deteriorated mentally, was restless and irritable and unable to work. He showed increasing signs of involvement of the pyramidal tracts and complained very much of paresthesia. The blood count at this time, confirmed by a second count the next day, showed a normal morphologic appearance and leukocyte count, but the color index was high, the red cells numbering 2,576,000 and the hemoglobin 70 per cent.

On April 9, 1923 it was reported that the paresthesia persisted and involved the hands, feet, legs and abdomen. He continually rubbed the thumb against the fingers. Strength was fairly good, but he showed a rather pronounced spastic paraplegia. There were no ataxia, no tremors and no cranial nerve palsies. Last year he took 30 drops of dilute hydrochloric acid with meals for several months after which he discontinued it. The blood count when examined showed red cells 2,768,000, hemoglobin, 73 per cent, differential leukocyte count normal, no nucleated red cells, slight anisocytosis, no poikilocytosis and no basophilic degeneration.

#### THE PATHOLOGY AND SYMPTOMATOLOGY OF COMBINED SCLEROSIS OF THE SPINAL CORD

Combined sclerosis of the spinal cord is characterized anatomically by degenerative lesions in the posterior and lateral columns and the affected areas are unlike those occurring in any other disease in that no neuroglial increase follows the degeneration. Collier, in his recent

a personal communication from Dr J F Wilkinson, of Melbourne, who found achlorhydria in a patient with digestive disturbances one year before the first sign of combined spinal sclerosis appeared

For purposes of control, Hurst and Bell made gastric analyses in a series of eight consecutive cases of disseminated sclerosis and nine consecutive cases of tabes dorsalis. In these seventeen cases, achlorhydria was not found, except in one tabetic person. When the well-known frequency of achylia gastrica is considered, no special importance can be attached to this one case out of seventeen. These authors say further:

In three recent cases, which presented features very suggestive of subacute combined degeneration, a normal curve of gastric acidity was discovered. Each eventually proved to be a case of syphilitic disease of the spinal cord. These cases are analogous with two others, the only cases in Guy's Hospital in which a diagnosis of Addison's anemia had been made in spite of the fact that free hydrochloric acid was present in the stomach. At the postmortem no evidence of hemolysis was present, one being found to have infective endocarditis, and the other, who died of lobar pneumonia, having microscopical changes in the spleen which were typical of Hodgkin's disease.

For the past several years, as indicated by the accompanying case histories, I have been greatly interested in my observation that achylia gastrica was an almost invariable finding in patients with acroparesthesias and symptoms of combined spinal sclerosis. In fact, this relationship impressed me as being as constant as the finding of achlorhydria in patients suffering from pernicious anemia. During this period, the diagnosis of combined spinal sclerosis was made in the case of one patient who showed free hydrochloric acid present in the gastric contents. This patient, however, was seen only once, and because of insufficient observation the opinion formed of his neurologic lesion was not considered conclusive. A certain proportion of persons with achylia gastrica have few, if any gastro-intestinal symptoms, and in five of the seven cases reported in this article it was the paresthesias, and not any abdominal complaint, that caused us to make the gastric analyses.

As is well known and illustrated by the case reports in this article, combined spinal sclerosis occurs in many persons who present no evidence of pernicious anemia. Woltmann<sup>2</sup> states that only one third of the patients suffering from subacute combined sclerosis of the spinal cord seen at the Mayo Clinic were found to have pernicious anemia, and quotes von Voss (1897) as finding about the same proportion of cases of pernicious anemia in a series of collected cases of combined spinal sclerosis. In my series of twenty-nine patients with combined spinal sclerosis, all of whom showed an achlorhydria, there were fourteen instances of unquestioned pernicious anemia. Several writers, among

hydrochloric acid in the gastric contents of 104 out of 107 patients suffering from pernicious anemia. Here, again, the older writers were inclined to attribute the achlorhydria to the anemia, and the view continues to be expressed that pernicious anemia causes gastric anacidity. That such an opinion is erroneous would seem, however, to be abundantly proved by the accumulated reports in the literature of cases in which it has been shown that persistent achylia gastrica precedes by months or years the onset of pernicious anemia, also, by the fact that the achlorhydria persists throughout periods of remission in pernicious anemia, and again by the fact that there is no constant curve of gastric secretion in other forms of severe anemia, and that the most pronounced secondary anemias, as a rule, do not show achlorhydria. Finally, and this seems conclusive, pernicious anemia has subsequently developed in certain patients following the artificial achylia induced by total gastrectomy for the relief of gastric carcinoma, without evidence of recurrence of the malignant disease. Such a case has been reported from the Mayo Clinic by Hartman,<sup>4</sup> and five such instances are mentioned by Hurst and Bell in their article referred to below. Already certain animal experiments are under way by my colleagues, Dr Haskell and Dr Courtney in the department of physiology of the Medical College of Virginia, to determine the blood changes that may follow total gastrectomy in dogs.

#### RELATIONSHIP OF ACHYLIA GASTRICA TO COMBINED SCLEROSIS OF THE SPINAL CORD

The relationship of achylia gastrica to pernicious anemia having been established, as well as the association of pernicious anemia with combined spinal sclerosis, it is strange that the relationship of achylia gastrica to combined spinal sclerosis was not noted long ago. Careful search of the literature failed to elicit any reference to this interesting association until recently when my attention was directed to the excellent and conclusive monograph of Arthur F. Hurst and J. R. Bell.<sup>5</sup> These authors report eight cases of combined spinal sclerosis, in all of which gastric analysis, by the fractional method, showed an absence of free hydrochloric acid. The test was repeated in three of the cases with the same result. They quote L. F. Barker<sup>6</sup> as having found complete achlorhydria in two cases of combined spinal sclerosis, and also mention

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4 Hartman, H. R. Blood Changes in a Gastrectomized Patient Simulating Those in Pernicious Anemia, *Am J M Sc* **162** 201, 1921

5 Hurst, A. F., and Bell, J. R. The Pathogenesis of Subacute Combined Degeneration of the Spinal Cord, with Special Reference to Its Connection with Addison's (Pernicious) Anemia, Achlorhydria and Intestinal Infection, *Brain* **45** pt 2, 266, 1922

6 Barker, L. F. Funicular Myelitis, or Combined Sclerosis of the Spinal Cord, *Med Clin of N America* **2** 1551, 1919

451 cases of achylia gastrica occurred in a series of 4,281 consecutive private patients subjected to gastric analysis, thus showing an incidence of 10.5 per cent.)

In other persons, however, toxins are evidently produced either from bacterial decomposition of the food that enters the intestines unprepared by the usual gastric digestion, or from bacteria from the mouth and throat that pass through the achylous stomach uninhibited by the acidity of the normal gastric juice. Of such toxins, one variety may have an especial affinity for the bone marrow or other hemopoietic organs and give rise to a hemolytic form of anemia, while another may exert its effect on the nervous tissues with a point of vulnerability in the posterior and lateral columns of the spinal cord. In one person the hemolytic toxin predominates, in another patient the neurotoxin is chiefly manifested, while in not a few cases there is evidence of a reaction to both toxins as is seen in the advanced case of pernicious anemia with cord changes.

The chief significance of this report of certain cases of combined sclerosis of the spinal cord associated with achylia gastrica, confirming abundantly the published findings of Hurst and Bell, is that it would seem to shed considerable light on the etiology of pernicious anemia. In combined spinal sclerosis we also find achlorhydria as an essential predisposing cause, a most constant factor that is lacking in certain other degenerative lesions of the spinal cord, such as disseminated sclerosis and tabes dorsalis. In fact, as Hurst and Bell emphasize, the presence of free hydrochloric acid in any fraction of a test meal is probably a decisive point against the diagnosis of combined spinal sclerosis in a doubtful case. The frequent association of combined sclerosis of the spinal cord and pernicious anemia would indicate that the absence of the protective power of the normal gastric juice may permit the elaboration of both a neurotoxin and a hemolytic toxin. Hence, combined spinal sclerosis and pernicious anemia may coexist in the same patient, or either disease may arise separately, depending on the character and amount of the toxins produced.

Many writers, especially those from Guy's Hospital, where Addison reported the first recorded cases of pernicious anemia, have emphasized the presence of oral sepsis in this disease ever since Hunter first drew attention to the subject over twenty years ago. Alveolar infection was noted in all of the eight cases of achlorhydria and combined spinal sclerosis reported by Hurst and Bell, and reference to my present cases shows that infection about the teeth was present in six of the seven patients. In this connection it may be significant to note that Hurst and Bell recovered a streptococcus from the duodenum with the Einhorn

them Cadwalader<sup>7</sup> have shown that continued observation of patients suffering from combined spinal sclerosis will demonstrate the subsequent development of the characteristic clinical and hematologic picture of pernicious anemia in a large proportion of the cases

#### THE PATHOGENESIS OF COMBINED SCLEROSIS OF THE SPINAL CORD

In the most authoritative description of subacute degeneration of the spinal cord by James Collie,<sup>1</sup> published as recently as 1921, it is stated that

Little is known of the causal factors of the disease, and in the majority of the recorded cases the patients have been strong and healthy until the onset of nervous symptoms. In a considerable number of cases, however, symptoms pointing to gastro-intestinal infection, such as vomiting, diarrhea, anorexia or constipation, have been prominent before the onset of the nervous symptoms

The failure of clinicians to recognize the almost invariable association of achylia gastrica with combined sclerosis of the spinal cord has, no doubt, been due, as Hurst and Bell point out, to the fact that this nervous disorder has been chiefly investigated by neurologists, who were only interested in a minor degree in the associated anemia or gastro-intestinal disturbances, while, on the other hand, the spinal changes observed in pernicious anemia have been investigated chiefly by physicians, whose interest was in the anemia rather than in the spinal disease. The significant feature of the monograph of Hurst and Bell is the fact that they discuss the two groups of cases, combined spinal sclerosis and pernicious anemia, from a common standpoint, and that they endeavor to show that both depend on the same underlying pathologic processes, namely, oral sepsis, absence of free hydrochloric acid from the stomach contents throughout digestion and consequent intestinal infection and intoxication

In spite of the expressed views of many writers who continue to reiterate the earlier confused state of our knowledge regarding the etiology of pernicious anemia, there is every reason to believe that achylia gastrica not only accompanies and precedes the development of this malady, but that it is an essential predisposing cause. The secretion of hydrochloric acid by the stomach is one of Nature's chemical defences against infection, and it is most probable that in all cases of persistent achylia gastrica there ensues, sooner or later, a chronic intestinal toxemia. This toxemia must be tolerated by many persons for long periods of time, as achlorhydria is a common finding (My

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<sup>7</sup> Cadwalader, W. B. Early Appearance of Symptoms of Combined Sclerosis of the Spinal Cord and Subsequent Development of Severe Anemia, *Pennsylvania M. J.* **24** 692, 1921

has a potential case of either pernicious anemia or combined sclerosis of the spinal cord. I am equally convinced that treatment, while encouraging in patients having paresthesias and symptoms of pyramidal tract degeneration without anemia, finds its greatest usefulness as a prophylactic measure. In other words, every person with an achlorhydria should receive regular and adequate amounts of hydrochloric acid with every meal, and this remedy should not be omitted or discontinued unless it can be shown by a subsequent gastric analysis that the stomach has renewed its secretory activity.

#### TREATMENT OF COMBINED SCLEROSIS OF THE SPINAL CORD AND THE ASSOCIATED ACHYLIA GASTRICA

The essential part of the treatment in every patient with achylia gastrica is the artificial replacement of the hydrochloric acid secretion in the stomach. This is readily accomplished by administering dilute hydrochloric acid with each meal. The matter of dosage is of much importance, and the pharmacopeal recommendation of 10 to 15 minims (0.6 to 0.9 cc) is obsolete and entirely inadequate. For the past fifteen years it has been my custom to order one teaspoonful of the official dilute hydrochloric acid, well diluted with each meal and after the introduction of the duodenal tube in making routine gastric analyses by the fractional method. I satisfied myself, experimentally, that this dose was sufficient. In certain cases, however, in addition to one teaspoonful of the acid with meals, I have ordered a second teaspoonful to be taken one-half hour after the meal. Hurst and Bell reproduce certain charts to illustrate that a dram and a half (5.85 gm) of dilute hydrochloric acid are required in order to compensate for the deficiency of gastric juice and state that the acid should be added in the proportion of 1 dram (3.9 gm) to 4 ounces (124.4 gm) of water in order to make a beverage, the acidity of which is about the same as that of gastric juice. The acid is best administered in buttermilk but may be taken in sweetened lemonade or orangeade, or in iced tea. It is a rather unpleasant dose in plain water. The acid-containing beverage is sipped during the course of the meal, and part of it may be reserved for the twenty or thirty minute period following the meal. The administration of pepsin, pancreatin or other digestive ferments, while quite appropriate, has never appeared to be of any special value and I rarely employ them in these cases. I have found that it is advisable to prohibit eating between meals except for indulgence in acid fruits, which may be taken freely. Buttermilk, either the natural article or milk which has been artificially soured with lactic acid bacilli, may also be taken at any time, and is not only well tolerated in cases of achlorhydria, but seems also to be particularly helpful.

tube in seven consecutive cases of pernicious anemia and in four consecutive cases of combined spinal sclerosis, while the same organism was recovered in only three out of twenty-six control cases

PROGNOSIS IN PERNICIOUS ANEMIA AND IN COMBINED  
SCLEROSIS OF THE SPINAL CORD

A point that should be emphasized is that true achylia gastrica is a persistent and probably permanent condition. I have had under frequent observation a woman, now 52 years old, in whom I first found an achlorhydria in January, 1909, and in whom fifteen consecutive gastric analyses in the intervening years have continued to show the absence of free hydrochloric acid. This patient has taken dilute hydrochloric acid in teaspoonful doses with meals regularly for the past fourteen years and has never shown any anemia or spinal cord changes. In common with all other clinicians, however, pernicious anemia has continued to be a fatal disease in my observation, with the possible exception of one most interesting patient who had an achylia gastrica in 1914, again in 1917, associated with a characteristic picture of pernicious anemia, intensive hydrochloric acid therapy since 1917, and a normal blood picture in 1923, although the achylia gastrica persists.

The outlook in cases of combined spinal sclerosis unassociated with pernicious anemia has impressed me as being much more favorable, that is, in those cases in which the achylia gastrica is recognized and appropriate treatment instituted. As mentioned in the foregoing, among the seven patients that form the basis of this article, one is subjectively cured, two are apparently well and one is greatly improved. These subjective results are particularly interesting in that the degenerative lesions in the spinal cord are probably permanent and the physical signs persist or gradually recede. Hurst and Bell state that sufficient time had not elapsed at the time of their publication to report the final results of treatment, but that in two of their cases there had been no increase in the nervous symptoms, and that in one of these patients the tingling of the feet and hands had almost disappeared and the ataxic and spastic gait had greatly improved, although the physical signs were unaltered.

These results in the expected outcome in combined sclerosis of the spinal cord are in striking contrast to the former views on this subject. In fact Collier in his authoritative monograph already referred to, writes in 1921, that "There is no evidence that recovery from this disease occurs in any of its stages."

Taking into consideration all the various factors already enumerated, I am firmly convinced that every person suffering from achylia gastrica

improved. There is good reason to believe that every person with true achylia gastrica has a potential case of either pernicious anemia or combined spinal sclerosis. More emphasis should be placed on the importance of adequate hydrochloric acid therapy as an essential prophylactic measure in every case of achylia gastrica.



Chronic foci of infection should always be sought for and eradicated if possible. Chronic infection in the gallbladder is a rather frequent associated lesion in patients with achlorhydria. Chronic cholecystitis was diagnosed in forty-nine of my 451 achylia cases, an incidence of 10.8 per cent, and was suspected in certain additional cases. Infection about the teeth and in the tonsils and accessory nasal sinuses, chronic appendicitis and chronic infection in the urinary tract are frequently to be found, and the possible special significance of oral sepsis has been emphasized above.

In combined sclerosis of the spinal cord, with the exception of the control of the associated achlorhydria, the treatment is purely symptomatic. Massage and graduated exercises may be employed, and sedatives may be used if necessary. Special treatment directed toward an accompanying anemia will not be discussed here, except to emphasize again that every person with a true achylia gastrica has a potential case of either pernicious anemia or combined sclerosis of the spinal cord, and that adequate treatment with hydrochloric acid in such instances is a prophylactic measure of the greatest value in combating the hemolytic toxins and neurotoxins that sooner or later become manifest in probably every case.

#### SUMMARY

In a study of 451 consecutive cases of achlorhydria, there were twenty-nine persons with definite evidence of combined sclerosis of the spinal cord. Of these twenty-nine patients, fourteen had pernicious anemia, one had pellagra and in seven the observations were incomplete, leaving seven patients that form the basis of this report.

Combined sclerosis of the spinal cord has been regarded as a disease of obscure etiology and hopeless prognosis. The study of these seven cases would seem to show, however, that achlorhydria not only precedes and accompanies the development of this nervous disorder, but that it is in all probability an essential predisposing cause. Achylia gastrica thus appears to be as constant a finding in combined spinal sclerosis as in pernicious anemia. In one instance neurotoxins, in the other hemolytic toxins, are evidently produced in the intestinal tract of the person whose stomach lacks the protective or inhibitory action of the normal hydrochloric acid secretion.

The prognosis in patients suffering from combined sclerosis of the spinal cord not accompanied by pernicious anemia, appears to be favorably influenced by persistent treatment with full doses of hydrochloric acid, together with the removal of such foci of chronic infection as may be found. Of the seven patients discussed in this report, one is subjectively cured, two are apparently well, and one is greatly

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RECOVERY RECORD FOR USE IN TUBERCULOSIS By GERALD B WEBB, M D, President, Colorado School of Tuberculosis, and CHARLES T RYDER, M D Cloth Price \$2.00 Pp 80 with 100 record forms attached New York Paul B Hoeber, Inc, 1923

Carefully written, optimistic throughout, admirably compiled, brief, accurate in its statements, none of which are so technical or involved as not to be easily comprehended by the average patient, and particularly offering a reasonable common sense explanation for each and every suggestion made, this volume should be helpful to both patient and physician

Any intelligent tuberculous patient would profit greatly by reading this book, and every patient who is being treated at home should have the opportunity to read and reread its contents The latter portion consists of weekly record charts for recording the temperature, pulse rate, weight, general notes, and questions to ask the physician during his visits There are enough of these charts to cover a period of two years

ENVIRONMENT AND RESISTANCE IN TUBERCULOSIS By ALLEN K KRAUSE, A M, M D, Editor-in-chief, The American Review of Tuberculosis Cloth, semi-flexible Price, \$1.50 Pp 144 Baltimore Williams & Wilkins Company, 1923

This book is divided into two sections one on environment, the other on resistance The first section—that on environment—is the revision of an address delivered in 1920 and published in the *American Review of Tuberculosis* in the same year It was originally prepared as part of a symposium on the topic “The Basic Cause of Breakdown with Tuberculosis Is it Malnutrition? Is it Heredity? Is it Environment?” The study of environment as an etiologic and determining factor in the development or progress of tuberculosis in an individual or community is discussed from the standpoint of nutrition, hygiene, occupation, family and social status, influence of trauma, intercurrent disease both acute and chronic, political and racial environment, etc

The major portion of the text is devoted to the subject of “Resistance,” and, likewise, is an elaboration of several addresses on “The Nature of Resistance to Tuberculosis,” all of which have been published in the *American Review of Tuberculosis* or the *Journal of the Outdoor Life* Specific and nonspecific factors concerned in resistance are thoroughly discussed In the first group the subject of allergy in tuberculosis is presented clearly and concisely, while in the second group the question of the nature etc of the tubercle, as well as the influence of ‘accidental factors,’ are considered from various angles

Physicians and others interested in the study and treatment of tuberculosis will find the author’s presentation of these important topics thorough and original

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